

To help keep you informed about medications in development, the *Walgreens Pipeline Report* provides a summary of specialty medications that may be approved by the FDA within the next few years. While not all-inclusive, this report focuses on medications in phase III studies that may impact treatment for certain specialty disease states or conditions. It also highlights select, newly approved or soon-to-be approved specialty medications of interest to the marketplace.

Medications to Watch

Here is a closer look at a few recently approved or soon-to-be approved medications that may have a significant impact on therapeutic classes and treatment for specific disease states and conditions.

Vismodegib

Vismodegib is currently under review by the FDA for the treatment of basal cell carcinoma (BCC). With an estimated annual incidence of 0.1 to 0.5 percent, BCC is the most common skin cancer in the United States. Most cases of BCC are cured with surgery, but in some cases there is progression to locally advanced or metastatic disease for which there is no standard treatment.

BCC is associated with mutations in the Hedgehog signaling pathway, which can lead to the uncontrolled growth of basal cells of the skin. Vismodegib is an orally administered Hedgehog signaling pathway inhibitor that prevents cell growth. In a phase II trial, 71 patients with locally advanced BCC and 33 patients with metastatic BCC were enrolled and received 150 mg of vismodegib once daily until disease progression. The primary endpoint of the trial was overall response rate (ORR) as assessed by independent review. Patients with locally advanced BCC had ORRs of 43 percent while patients with metastatic BCC had ORRs of 30 percent. The most common adverse events reported in this trial were muscle spasms, hair loss, taste disturbance, weight loss and fatigue.

Genentech filed a new drug application (NDA) for vismodegib in September 2011. The FDA accepted the filing and granted priority review status in November

2011. A response to the NDA is expected in March 2012.

Mulsevo® (semuloparin)

Sanofi-aventis has submitted an NDA for Mulsevo® (semuloparin) for the prevention of venous thromboembolism (VTE) events in cancer patients initiating chemotherapy. VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE), occurs in 4 percent to 20 percent of patients with cancer. In one study, researchers found a 4-fold greater risk of VTE in patients with cancer which was further increased to a 6.5-fold risk in those patients receiving chemotherapy. Mulsevo is an ultra-low molecular weight heparin that inhibits factor Xa in the coagulation cascade and helps prevent clot formation.

In a phase III, double-blind, placebo-controlled trial, 3,212 patients initiating a new chemotherapy course for metastatic or locally advanced solid tumors (lung, colon-rectum, stomach, ovary, pancreas or bladder cancer) were enrolled and randomized to receive 20 mg subcutaneous Mulsevo once daily or placebo until change in the chemotherapy course. The primary endpoint of the trial was the composite of any symptomatic DVT, non-fatal PE and VTE-related death. The median duration of treatment was approximately 3.5 months, with 20 of the 1,608 patients (1.2 percent) in the Mulsevo group and 55 of

the 1,604 patients (3.4 percent) in the placebo group experiencing a thromboembolic event. This difference represents a 64 percent risk reduction for a thromboembolic event in patients receiving Mulsevo. Clinically relevant bleeding was observed in 2.8 percent of Mulsevo patients and 2 percent of placebo patients.

The NDA for Mulsevo was filed in September 2011. A response to the NDA is expected in July 2012.

Tofacitinib

Pfizer has developed tofacitinib for the treatment of rheumatoid arthritis (RA) and psoriasis. Tofacitinib is an orally administered Janus-associated kinase (JAK) inhibitor that interferes with inflammatory and immune responses.

Pfizer has completed a number of phase III trials to examine the efficacy of tofacitinib in patients with moderately to severely active RA. Primary endpoints of these trials included ACR20 responder rate, change from baseline in the Health Assessment Questionnaire Disability Index (HAQ-DI) and the rate of patients achieving a Disease Activity Score 28 (DAS28) of less than 2.6 (indicating disease remission).

In a six-month trial, 611 patients with an inadequate response to a traditional or biological disease-modifying antirheumatic drug (DMARD) were randomized to receive monotherapy with tofacitinib 5 mg or 10 mg twice daily or placebo. Two of the primary endpoints for both doses of tofacitinib were achieved, including ACR20 responder rate and mean change in HAQ-DI. One twelve-month trial also

enrolled patients with an inadequate response to a traditional or biological DMARD. These 792 patients received tofacitinib 5 mg or 10 mg twice daily or placebo in addition to a traditional DMARD. In this trial, all primary endpoints for both doses of tofacitinib were met.

Another 12-month trial enrolled 717 patients who had an inadequate response to methotrexate (MTX). All patients remained on MTX and were randomized to receive tofacitinib 5 mg or 10 mg twice daily, Humira® (adalimumab) 40 mg subcutaneous injection every two weeks or placebo. Both doses of tofacitinib met all primary endpoints compared to placebo. The primary endpoint results were similar for tofacitinib and Humira; however, the trial was not designed to directly compare these two treatments. A six-month trial was conducted in 399 patients who had an inadequate response to tumor necrosis factor (TNF)-inhibitor therapy. Patients received tofacitinib 5 mg or 10 mg twice daily or placebo in addition to MTX. In this trial, both doses of tofacitinib also met all three primary endpoints compared to placebo.

Adverse events reported in the trials include infections, decreased neutrophil counts, increased cholesterol levels and increased serum creatinine.

In December 2011, the FDA accepted for review the NDA for tofacitinib in the treatment of RA. A response to the NDA is expected in August 2012.

Medications Recently Approved

Manufacturer/ Drug Name	Indication	Mechanism of Action/Drug Class	Route of Administration	Approval Date	Comments
Growth Disorders					
Sandoz/Omnitrope® (somatropin)	For the treatment of growth failure associated with Turner syndrome	Replaces growth hormone/ Recombinant human growth hormone	SC injection	9/1/2011	Now approved for all of the same indications as the reference product, Genotropin® (somatropin)
Hemolytic Uremic Syndrome					
Alexion Pharmaceuticals/Soliris® (eculizumab)	For the treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy	Prevents the final stages of complement activation, thereby reducing red blood cell destruction/ Complement inhibitor	Intravenous (IV) infusion	9/23/2011	Previously approved for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis
Oncology					
Amgen/Prolia® (denosumab)	As a treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer and in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer	Inhibits bone destruction/RANKL (receptor activator of nuclear factor kappa-B ligand) inhibitor	SC injection	9/16/2011	Previously approved for the treatment of postmenopausal women with osteoporosis at high risk for fracture Also approved under the trade name Xgeva® for the prevention of skeletal-related events in patients with bone metastases from solid tumors
EUSA Pharma/ Erwinaze® (asparaginase <i>Erwinia chrysanthemi</i>)	As a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to <i>E. coli</i> -derived asparaginase	Depletes the level of asparagine in the bloodstream, which is essential for cell growth/ Asparaginase enzyme	Intramuscular (IM) injection	11/18/2011	First treatment option approved for patients with hypersensitivity to <i>E. coli</i> -derived asparaginase
Incyte Corporation/ Jakafi™ (ruxolitinib)	For treatment of patients with intermediate- or high-risk myelofibrosis (MF), including primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF	Inhibits JAK1 and JAK2, which are involved in the formation and development of blood cells/JAK inhibitor	Oral	11/16/2011	First medication approved for the treatment of MF

Medications Recently Approved (continued)

Manufacturer/ Drug Name	Indication	Mechanism of Action/Drug Class	Route of Administration	Approval Date	Comments
Ophthalmology					
Regeneron Pharmaceuticals/ Eylea™ (aflibercept)	For the treatment of patients with neovascular age-related macular degeneration (AMD)	Binds vascular endothelial growth factor (VEGF) and placental growth factor/ Antiangiogenesis inhibitor	Intravitreal injection	11/18/2011	Following three initial monthly injections, Eylea is administered once every eight weeks

Pipeline Medications in Phase III Trials

Manufacturer/ Drug Name	Indication	Mechanism of Action/Drug Class	Route of Administration	Comments
Amyloidosis				
Pfizer/Tafamidis	For the treatment of transthyretin (TTR) familial amyloid polyneuropathy	Inhibits TTR amyloid fibril formation/TTR stabilizer	Oral	<ul style="list-style-type: none"> • Designated as an orphan drug with fast track status • NDA filed February 2011 • Received a refusal to file letter from the FDA in April 2011 • Working to resubmit the NDA
Anemia				
Affymax and Takeda/ Peginesatide	For the treatment of anemia in patients with chronic renal failure who are on dialysis	Binds to and activates the erythropoietin receptor/Erythropoiesis stimulating agent	Injection	<ul style="list-style-type: none"> • Administered once every four weeks in clinical trials • NDA filed May 2011 • A response to the NDA is expected March 2012
Bleeding Disorders				
Novo Nordisk/ Recombinant factor XIII (NN1841)	For the treatment of congenital factor XIII deficiency	Replaces deficient factor/Factor replacement therapy	IV infusion	<ul style="list-style-type: none"> • Biologics license application (BLA) filed February 2011 • A response to the BLA is expected December 2011
Coagulation Disorders				
Sanofi-aventis/ Mulsevo® (semuloparin)	For the prevention of VTE events in cancer patients initiating chemotherapy	Inhibits factor Xa/Ultra-low molecular weight heparin	SC injection	<ul style="list-style-type: none"> • NDA filed September 2011 • A response to the NDA is expected July 2012
Cystic Fibrosis (CF)				
Vertex Pharmaceuticals/ Kalydeco™ (ivacaftor, VX-770)	For the treatment of CF in patients ages 6 and older who have at least one copy of the G551D mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene	Increases chloride ion transport across cell membranes/ CFTR potentiator	Oral	<ul style="list-style-type: none"> • Designated as an orphan drug with fast track status • NDA filed October 2011 • FDA granted priority review December 2011 • A response to the NDA is expected April 2012

Pipeline Medications in Phase III Trials (continued)

Manufacturer/ Drug Name	Indication	Mechanism of Action/Drug Class	Route of Administration	Comments
Fertility				
Merck/Corifollitropin alfa	For the development of multiple follicles and pregnancy in women participating in an assisted reproductive technology program	Stimulates ovarian follicular growth/ Sustained follicle stimulant	SC injection	<ul style="list-style-type: none"> Primary endpoints achieved in phase III trial July 2009 BLA filing anticipated in 2012
Hepatitis				
Tibotec Pharmaceuticals/ TMC435	In combination with peginterferon and ribavirin for the treatment of chronic hepatitis C virus infection in treatment-naïve and treatment-failure patients	Prevents virus replication/Protease inhibitor	Oral	<ul style="list-style-type: none"> FDA granted fast track status Completed enrollment of three phase III trials August 2011
Hereditary Angioedema (HAE)				
Pharming Group NV and Santarus/ Rhucin® (C1 inhibitor)	For the treatment of acute attacks in patients with HAE	Replaces deficient C1 inhibitor/C1 inhibitor replacement therapy	IV infusion	<ul style="list-style-type: none"> Designated as an orphan drug BLA filed December 2010 Received a refusal to file letter from the FDA in February 2011 Based on a meeting with the FDA, the companies have revised the protocol for the phase III trial to support the BLA; the trial should be completed by the end of 2012
Human Immunodeficiency Virus (HIV)				
Gilead Sciences/ Quad (elvitegravir, cobicistat, emtricitabine and tenofovir)	For the treatment of HIV infection	Prevents virus replication/Integrase inhibitor, boosting agent, nucleoside reverse transcriptase inhibitor and nucleotide reverse transcriptase inhibitor	Oral	<ul style="list-style-type: none"> Once-daily, single-tablet regimen NDA filed October 2011
Gilead Sciences/ Elvitegravir	For the treatment of HIV in treatment-experienced patients	Prevents virus replication/Integrase inhibitor	Oral	<ul style="list-style-type: none"> Primary endpoint achieved in phase III trial March 2011 NDA filing planned for 2012
Huntington's Disease (HD)				
NeuroSearch/ Huntexil® (pridopidine)	For the treatment of HD	Enhances or inhibits dopamine-dependent functions in the brain/ Dopaminergic stabilizer	Oral	<ul style="list-style-type: none"> Designated as an orphan drug New phase III trial to begin in the first half of 2012

Pipeline Medications in Phase III Trials (continued)

Manufacturer/ Drug Name	Indication	Mechanism of Action/Drug Class	Route of Administration	Comments
Inflammatory Diseases				
AstraZeneca/ Fostamatinib	For the treatment of RA	Blocks signaling in multiple cell types involved in inflammation and tissue degradation/ Spleen tyrosine kinase (Syk) inhibitor	Oral	<ul style="list-style-type: none"> Recruiting for three phase III studies NDA filing planned for 2013
Pfizer/Tofacitinib	For the treatment of RA and psoriasis	Interferes with the inflammatory and immune responses/ JAK inhibitor	Oral	<ul style="list-style-type: none"> NDA filing for RA accepted December 2011 A response to the NDA is expected August 2012
Lysosomal Storage Diseases				
Amicus Therapeutics and GlaxoSmithKline/ Amigal (migalastat)	For the treatment of Fabry disease	Binds to and stabilizes alpha-galactosidase/ Alpha-galactosidase A enhancer	Oral	<ul style="list-style-type: none"> Designated as an orphan drug Enrollment in first phase III trial expected to be completed in the fourth quarter of 2011 Second phase III trial initiated in the third quarter of 2011
Protalix/Uplyso (taliglucerase alfa)	For the treatment of Gaucher disease	Replaces deficient glucocerebrosidase/ Enzyme replacement therapy	IV infusion	<ul style="list-style-type: none"> Designated as an orphan drug NDA filed December 2009 Received a complete response letter February 2011 FDA accepted resubmission of NDA August 2011 A response to the NDA was expected February 2012; however, the FDA required additional time to review; a response is now expected May 2012
Shire/Replagal® (agalsidase alfa)	For the treatment of Fabry disease	Replaces deficient alpha- galactosidase A/Enzyme replacement therapy	IV infusion	<ul style="list-style-type: none"> Designated as an orphan drug with fast track status Initiated a rolling BLA October 2011
Multiple Sclerosis (MS)				
Biogen Idec/BG-12 (dimethyl fumarate)	For the treatment of relapsing- remitting MS	Activates the Nrf2 transcriptional pathway, which regulates the antioxidant response/Gene transcription modulator	Oral	<ul style="list-style-type: none"> Primary endpoint achieved in second phase III trial October 2011 NDA filing anticipated in 2012
Sanofi-aventis/ Aubagio™ (teriflunomide)	For the treatment of relapsing forms of MS	Inhibits pyrimidine synthesis/ Immunomodulatory agent	Oral	<ul style="list-style-type: none"> NDA filed August 2011 A response to the NDA is expected June 2012
Teva/Laquininmod	For the treatment of relapsing- remitting MS	Inhibits autoimmune and inflammatory disease activity/ Immunomodulatory agent	Oral	<ul style="list-style-type: none"> Teva met with the FDA to discuss a regulatory path towards approval in the third quarter 2011 Based on the meeting, Teva will conduct another phase III trial before filing for approval

Pipeline Medications in Phase III Trials (continued)

Manufacturer/ Drug Name	Indication	Mechanism of Action/Drug Class	Route of Administration	Comments
Neuroendocrine Disorders				
Novartis/Pasireotide (SOM230)	For the treatment of Cushing's disease, carcinoid syndrome and acromegaly	Binds somatostatin receptors/Somatostatin analogue	SC injection	<ul style="list-style-type: none"> Designated as an orphan drug NDA filed for Cushing's disease in June 2011 was withdrawn due to an issue related to the chemistry, manufacturing and controls section; the application will be resubmitted following further discussions with the FDA
Neurogenic Disorders				
Chelsea Therapeutics/ Northera™ (droxidopa)	For the treatment of symptomatic neurogenic orthostatic hypotension in patients with primary autonomic failure, dopamine beta hydroxylase deficiency and non-diabetic autonomic neuropathy	Increases norepinephrine levels in the nervous system/Synthetic catecholamine	Oral	<ul style="list-style-type: none"> Designated as an orphan drug with fast track status NDA filed September 2011 FDA granted priority review November 2011 A response to the NDA is expected March 2012
Oncology				
Agennix/Talactoferrin	For the third-line treatment of non-small cell lung cancer (NSCLC)	Stimulates immune system to destroy cancer cells/Dendritic cell recruiter and activator	Oral	<ul style="list-style-type: none"> Designated as an orphan drug with fast track status Results from phase III trial expected in the first half of 2012
AVEO Pharmaceuticals and Astellas/Tivozanib	For the treatment of advanced renal cell carcinoma (RCC)	Reduces tumor cell growth and blood supply/ VEGF receptor inhibitor	Oral	<ul style="list-style-type: none"> Results of phase III trial expected in the first quarter of 2012
Bayer HealthCare/ Alpharadin (radium-223 chloride)	For the treatment of patients with castrate-resistant prostate cancer (CRPC) and bone metastases	Mimics the behavior of calcium in the bone to target areas of high bone turnover in and around bone metastases/Alpha-pharmaceutical	IV infusion	<ul style="list-style-type: none"> FDA granted fast track status Primary endpoint achieved in phase III trial June 2011 First regulatory submission planned for mid-2012
Bristol-Myers Squibb/ Brivanib	For the treatment of advanced hepatocellular carcinoma in patients who have failed or are intolerant to Nexavar® (sorafenib)	Reduces tumor cell growth and blood supply/ VEGF receptor and fibroblast growth factor receptor inhibitor	Oral	<ul style="list-style-type: none"> Results of phase III trial expected in 2011 NDA filing planned for 2012
Cell Therapeutics/ Opaxio™ (paclitaxel poliglumex)	For the treatment of ovarian cancer	Promotes assembly and stabilizes microtubules, resulting in inhibition of cellular division/ Antimicrotubule chemotherapy agent	IV infusion	<ul style="list-style-type: none"> Links paclitaxel to a biodegradable polyglutamate polymer that delivers more chemotherapy to tumor cells Interim analysis of phase III trial may be available in mid-2012

Pipeline Medications in Phase III Trials (continued)

Manufacturer/ Drug Name	Indication	Mechanism of Action/Drug Class	Route of Administration	Comments
Oncology				
Cell Therapeutics/ Pixuvri™ (pixantrone)	For the treatment of relapsed or refractory aggressive non-Hodgkin lymphoma (NHL)	Damages the DNA of cancer cells, resulting in cancer cell death/ Topoisomerase II inhibitor	IV infusion	<ul style="list-style-type: none"> Designed to reduce the potential for heart damage, compared with current anthracyclines NDA filed June 2009 Received a complete response letter April 2010 Resubmitted NDA October 2011 A response to the NDA is expected April 2012
ChemGenex Pharmaceuticals/ Omapro™ (omacetaxine)	For the treatment of chronic myeloid leukemia (CML) in patients who failed treatment with two or more tyrosine-kinase inhibitors (TKIs)	Inhibits protein translation of oncoproteins/Cetaxine	SC injection	<ul style="list-style-type: none"> Designated as an orphan drug with fast track status NDA filing planned for the second half of 2011
EpiCept/Ceplene® (histamine dihydrochloride)	In conjunction with interleukin (IL)-2 for remission maintenance in patients with acute myeloid leukemia (AML)	Protects the lymphocytes responsible for destroying leukemia cells/Histamine analogue	SC injection	<ul style="list-style-type: none"> Designated as an orphan drug NDA filed June 2010 Received a refusal to file letter from the FDA August 2010 Plans to file a revised protocol for a phase III confirmatory trial with the FDA in the first quarter of 2012
Exelixis/Cabozantinib	For the treatment of medullary thyroid cancer	Inhibits cell growth and survival/TKI	Oral	<ul style="list-style-type: none"> Designated as an orphan drug with fast track status Requesting permission to begin a rolling NDA submission
Genentech/ Vismodegib	For the treatment of BCC	Inhibits cell growth/ Hedgehog signaling pathway inhibitor	Oral	<ul style="list-style-type: none"> NDA filed September 2011 FDA granted priority review November 2011 A response to the NDA is expected March 2012
Merck/Ridaforolimus (MK-8669)	For the treatment of metastatic soft tissue and bone sarcomas	Inhibits tumor cell growth and the formation of new blood vessels/ Mammalian target of rapamycin inhibitor	Oral	<ul style="list-style-type: none"> Designated as an orphan drug with fast track status NDA filed August 2011 A response to the NDA is expected June 2012

Pipeline Medications in Phase III Trials (continued)

Manufacturer/ Drug Name	Indication	Mechanism of Action/Drug Class	Route of Administration	Comments
Oncology				
Novartis/Faridak [®] (panobinostat)	For the treatment of Hodgkin lymphoma in patients who have relapsed or become refractory after a stem cell transplant	Inhibits tumor cell growth, causes cell death and inhibits the formation of new blood vessels/ Histone deacetylase inhibitor	Oral	<ul style="list-style-type: none"> Designated as an orphan drug NDA filed December 2010 Received a refusal to file letter from the FDA in 2011
Onyx Pharmaceuticals/ Carfilzomib	For the treatment of relapsed and/or refractory multiple myeloma	Causes cell death/ Proteasome inhibitor	IV injection	<ul style="list-style-type: none"> Designated as an orphan drug with fast track status Rolling NDA completed September 2011
Pfizer/Inlyta (axitinib)	For the treatment of advanced RCC	Reduces tumor cell growth and blood supply/ VEGF receptor inhibitor	Oral	NDA filing accepted June 2011
Pfizer/Bosutinib	For the treatment of newly diagnosed CML	Reduces tumor cell growth and blood supply/Src and Abl kinase inhibitor	Oral	NDA filing planned for 2011
Regeneron and Bayer HealthCare/ Zaltrap [™] (afibercept)	For the treatment of metastatic colorectal cancer	Binds VEGF and placental growth factor/ Antiangiogenesis inhibitor	IV infusion	BLA filed October 2011
Roche/Pertuzumab	In combination with Herceptin [®] (trastuzumab) and docetaxel for the treatment of HER2-positive metastatic breast cancer	Prevents the HER2 receptor from pairing with other HER receptors/ HER2 dimerization inhibitor	IV infusion	<ul style="list-style-type: none"> Primary endpoint achieved in phase III study July 2011 BLA filing planned for December 2011
Ophthalmology				
ThromboGenics/ Ocriplasmin	For the treatment of symptomatic vitreomacular adhesion including macular holes	Targets the fibronectin, laminin and type IV collagen fibers that adhere the vitreous to the retina/Proteolytic enzyme	Intravitreal injection	<ul style="list-style-type: none"> Primary endpoints achieved in two phase III trials in 2010 Regulatory filing planned for the end of 2011
Primary Immunodeficiency				
Baxter and Halozyme/HyQ	Replacement therapy for primary immunodeficiency	Replaces deficient immunoglobulin/ Replacement therapy	SC infusion	<ul style="list-style-type: none"> HyQ contains recombinant human hyaluronidase, which facilitates the dispersion and absorption of the immunoglobulin BLA filed July 2011
Biotest/Bivigam [™]	Replacement therapy for primary immunodeficiency	Replaces deficient immunoglobulin/ Replacement therapy	IV infusion	<ul style="list-style-type: none"> BLA filed November 2010 A response to the BLA is expected by the end 2011
Short Bowel Syndrome (SBS)				
NPS Pharmaceuticals/ Gattex [®] (teduglutide)	For the treatment of SBS by reducing patients' dependence on IV feeding	Promotes gastrointestinal regeneration/Analogue of glucagon-like peptide-2	SC injection	<ul style="list-style-type: none"> Designated as an orphan drug Rolling BLA completed December 2011

New Dosage Forms in the Pipeline

Manufacturer/ Drug Name	Indication	Mechanism of Action/Drug Class	Current Route of Administration	Investigational Route of Administration*	Comments
Cystic Fibrosis (CF)					
Pharmaxis/Bronchitol (mannitol)	For the treatment of CF	Hydrates the lungs/Osmotic diuretic	IV infusion, inhalation	Inhalation	NDA filing planned for 2012
Multiple Sclerosis (MS)					
Biogen Idec and Abbott/ Daclizumab HYP (high- yield process)	For the treatment of relapsing- remitting MS	Binds to the CD25 receptor on T cells/ Therapeutic antibody	IV infusion	SC injection	<ul style="list-style-type: none"> Phase III trial currently enrolling participants Marketed as Zenapax® for the prevention of acute kidney rejection
Oncology					
ADVENTRX/Exelbine™ (vinorelbine emulsion)	For the first-line treatment of unresectable, advanced NSCLC	Inhibits microtubule formation/Vinca alkaloid	IV injection	IV injection	<ul style="list-style-type: none"> Same active ingredient as Navelbine® (vinorelbine) Designed to reduce the incidence and severity of vein irritation associated with IV administration Received a complete response letter August 2011 Plan to seek a partner or outside investor to continue development
Millennium/Velcade® (bortezomib)	For the treatment of multiple myeloma	Causes cell death/ Proteasome inhibitor	IV injection	SC injection	<ul style="list-style-type: none"> IV formulation also approved for the treatment of mantle cell lymphoma Supplemental new drug application (sNDA) filed April 2011
Roche/ Herceptin® (trastuzumab)	For the treatment of HER2-positive early breast cancer	Inhibits the proliferation of tumor cells that overexpress HER2/ Monoclonal antibody	IV infusion	SC injection	<ul style="list-style-type: none"> Co-primary endpoints achieved in phase III trial October 2011 First regulatory filing planned for 2012
Talon Therapeutics/ Marqibo® (vincristine sulfate in liposomes)	For the treatment of relapsed or refractory ALL	Inhibits microtubule formation/Vinca alkaloid	IV infusion	IV infusion	<ul style="list-style-type: none"> Encapsulated formulation of vincristine NDA filed July 2011 A response to the NDA is expected May 2012
Pulmonary Arterial Hypertension (PAH)					
United Therapeutics/ Oral treprostinil	For the treatment of PAH	Dilates pulmonary blood vessels/ Prostacyclin analogue	Continuous SC or IV infusion and inhalation	Oral	NDA filing planned for the first quarter of 2012

*Dosage form is not available. Only investigational route of administration is available at this time.

New Indications in the Pipeline

Manufacturer/ Drug Name	Current Indication	Investigational Indication	Mechanism of Action/Drug Class	Route of Administration	Comments
Fertility					
Columbia Laboratories/ Prochieve® (progesterone gel)	For progesterone supplementation or replacement as part of an assisted reproductive technology treatment for infertile women with progesterone deficiency	To reduce the risk of preterm birth in women with short uterine cervical length in the mid-trimester of pregnancy	Helps maintain pregnancy/ Progesterone supplement	Vaginally	<ul style="list-style-type: none"> • NDA filed April 2011 • A response to the NDA is expected February 2012
Inflammatory Diseases					
Abbott/Humira® (adalimumab)	For the treatment of RA, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease and plaque psoriasis	For the treatment of moderate to severe ulcerative colitis	Targets TNF alpha, which is involved in the inflammatory process/TNF inhibitor	SC injection	Supplemental biologics license application (sBLA) filed in 2011
Novartis/Illaris® (canakinumab)	For the treatment of cryopyrin-associated periodic syndromes (CAPS)	For the treatment of refractory acute gout flares	Targets IL-1 beta/ IL-1 beta inhibitor	SC injection	<ul style="list-style-type: none"> • sBLA filed in the first quarter of 2011 • Received a complete response letter August 2011; the FDA requested additional information
Regeneron Pharmaceuticals/ Arcalyst® (rilonacept)	For the treatment of CAPS, including familial cold autoinflammatory syndrome and Muckle-Wells syndrome	For the prevention of gout flares in patients initiating uric acid-lowering therapy	Binds and neutralizes IL-1/ Long-acting IL-1 inhibitor	SC injection	<ul style="list-style-type: none"> • sBLA filed September 2011 • A response to the sBLA is expected July 2012
Multiple Sclerosis (MS)					
Genzyme/ Lemtrada™ (alemtuzumab)	For the treatment of B-cell chronic lymphocytic leukemia (CLL)	For the treatment of relapsing-remitting MS	Binds to the CD52 antigen on B cells and T cells/ Therapeutic antibody	IV infusion	<ul style="list-style-type: none"> • FDA granted fast track status • Co-primary endpoints achieved in second phase III trial November 2011 • sBLA filing planned for the first quarter of 2012 • Marketed as Campath® for CLL indication

New Indications in the Pipeline (continued)

Manufacturer/ Drug Name	Current Indication	Investigational Indication	Mechanism of Action/Drug Class	Route of Administration	Comments
Oncology					
Amgen/Xgeva [®] (denosumab)	For the prevention of skeletal-related events in patients with bone metastases from solid tumors	For the treatment of men with CRPC to reduce the risk of bone metastases	Inhibits bone destruction/ RANKL inhibitor	SC injection	<ul style="list-style-type: none"> • sBLA filed June 2011 • A response to the sBLA is expected April 2012
Eisai/Dacogen [®] (decitabine)	For the treatment of myelodysplastic syndromes	For the treatment of elderly patients with AML	Restores normal function to genes that control how cells develop and grow/ Demethylating agent	IV infusion	<ul style="list-style-type: none"> • sNDA filed May 2011 • A response to the sNDA is expected March 2012
GlaxoSmithKline/ Votrient [®] (pazopanib)	For the treatment of advanced RCC	For the treatment of advanced soft tissue sarcoma	Reduces tumor cell growth and blood supply/TKI	Oral	<ul style="list-style-type: none"> • sNDA filed June 2011 • A response to the sNDA is expected April 2012
Millennium/ Velcade [®] (bortezomib)	For the treatment of multiple myeloma and mantle cell lymphoma	In combination with Rituxan [®] (rituximab) for the treatment of relapsed follicular NHL	Causes cell death/ Proteasome inhibitor	IV injection	<ul style="list-style-type: none"> • sNDA filed April 2011 • sNDA withdrawn October 2011 based upon discussions with external advisors and the FDA
Novartis/ Afinitor [®] (everolimus)	For the treatment of advanced RCC, progressive neuroendocrine tumors of pancreatic origin and subependymal giant cell astrocytoma associated with tuberous sclerosis	For the treatment of angiomyolipoma associated with tuberous sclerosis complex In combination with Aromasin [®] (exemestane) for the treatment of ER+HER2-breast cancer	Inhibits tumor cell growth and the formation of new blood vessels/ Mammalian target of rapamycin (mTOR) inhibitor	Oral	<ul style="list-style-type: none"> • Primary endpoints met in phase III trials for both indications September 2011 • sNDA filings planned for the end of 2011
Novartis/ Tasigna [®] (nilotinib)	For the treatment of chronic and accelerated-phase Philadelphia chromosome-positive (Ph+) CML in patients resistant or intolerant to prior therapy that included Gleevec, and for the first-line treatment of Ph+ CML	For the treatment of c-Kit-positive melanoma	Inhibits Bcr-Abl kinase/TKI	Oral	<ul style="list-style-type: none"> • sNDA planned for 2014

New Indications in the Pipeline (continued)

Manufacturer/ Drug Name	Current Indication	Investigational Indication	Mechanism of Action/Drug Class	Route of Administration	Comments
Pulmonary Arterial Hypertension (PAH)					
Novartis/ Gleevec® (imatinib)	For the treatment of CML, ALL, myelodysplastic/ myeloproliferative diseases, aggressive systemic mastocytosis, hypereosinophilic syndrome, chronic eosinophilic leukemia, dermatofibrosarcoma protuberans and gastrointestinal stromal tumors	For the treatment of PAH	Improves pulmonary vascular resistance and increases cardiac output/TKI	Oral	<ul style="list-style-type: none"> • Primary endpoint achieved in phase III trial September 2011 • First regulatory submission planned for 2011

Glossary of Terms

Accelerated approval – allows pharmaceutical companies to obtain approval for products based on less clinical data than typically required for a normal approval, and is used for patients considered to have unmet medical needs.

Approvable letter – term used when assessing NDAs which indicated that a medication could probably be approved at a later date, provided that the applicant supplied requested information to the FDA or made specified changes. Since August 11, 2008, the FDA has issued a complete response letter to the applicant in place of an approvable letter.

BLA – stands for “Biologics License Application,” similar to an NDA, but used for investigational medications that are considered to be biologic agents.

Complete response letter – issued to let the applicant know that the review period for an investigational agent is complete and that the NDA or BLA is not yet ready for approval.

Cystic fibrosis – CF.

Double-blind trial – a type of study in which the participants and the investigators are blinded to treatment; this type of study has less bias than nonblinded studies.

Expanded access program – manufacturer programs that allow the distribution of new medications prior to FDA approval for patients with a life-threatening condition who cannot be treated successfully with currently available medications.

Fast track status – designation granted by the FDA to an investigational agent indicating an expedited review of the NDA or BLA; usually applies to medications that treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs.

Hereditary angioedema – HAE.

Multiple sclerosis – MS.

NDA – stands for “New Drug Application,” the process by which a manufacturer submits information to the FDA to gain approval for the agent; conducted after phase III development is completed.

Nonapprovable letter – term used when assessing NDAs which indicated that the application had deficiencies that generally required the submission of substantial data before the application could be approved. Since August 11, 2008, the FDA has issued a complete response letter to the applicant in place of a nonapprovable letter.

Orphan drug – a medication that treats a rare disease that affects fewer than 200,000 Americans. A medication granted orphan drug status is entitled to seven years of marketing exclusivity.

Phase II – second phase of medication development; typically involves several hundred patients to determine safety and preliminary data on efficacy.

Phase III – last phase of medication development; involves safety and efficacy trials of the new medication. This phase of development can take years to complete.

Priority review – designation granted by the FDA to an investigational agent after it has been submitted to the FDA for approval; a priority designation means that the FDA will review and take action on the application (approve or not approve) within six months instead of the standard 10 months for all other medication filings.

Pulmonary arterial hypertension – PAH.

Randomized controlled trial – a study in which people are allocated at random (by chance alone) to receive one of several clinical interventions; it is the most powerful study design in clinical research.

Refusal to file letter – a letter the FDA issues to the applicant if it determines the application is not sufficiently complete.

Rheumatoid arthritis – RA.

Risk evaluation and mitigation strategy (REMS) – a strategy to manage a known or potential serious risk associated with a drug or biological product. This strategy will be required if the FDA finds that a REMS is necessary to ensure that the benefits of the drug or biological product outweigh its risks.

Rolling submission – usually applies to fast track medications; indicates that the review process can be started even before the FDA receives all the information. However, the FDA requires all the information before a final decision about approval can be made.

sBLA – stands for “Supplemental Biologics License Application,” similar to sNDA, but used for already approved investigational medications that are considered to be biologic agents.

sNDA – stands for “Supplemental New Drug Application,” the process by which a pharmaceutical company submits information to the FDA to gain approval for a new indication for an agent that has already been approved by the FDA.

SPA – stands for “Special Protocol Assessment,” an agreement with the FDA that the manufacturer’s clinical protocol for a phase III trial is acceptable to support an NDA or BLA.

Treatment-naive – patients who have never been treated before for a particular condition.

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