

# Specialty Pharmacy Pipeline Report

Third Quarter 2008

To help keep you informed about medications in development, the *Walgreens Specialty Pharmacy 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 selected, 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.

### Berinert<sup>®</sup> P and Cinryze<sup>™</sup> (C1 inhibitor)

Berinert<sup>®</sup> P and Cinryze<sup>™</sup> are two new medications in development for the treatment of hereditary angioedema (HAE). HAE is a rare, potentially fatal genetic disorder caused by a deficiency or dysfunction of the plasma protein C1 inhibitor. There are an estimated 10,000 people in the United States with HAE. Patients experience swelling attacks typically involving the extremities, face, urogenital tract and upper airway. Swelling in the wall of the bowel can also occur, leading to severe abdominal pain that may also be accompanied by nausea and vomiting. The frequency and severity of attacks varies significantly among patients and often there is not a clear initiating cause for the attack.

Therapy for HAE is usually divided into three types: chronic long-term prophylaxis, short-term prophylaxis and treatment of acute attacks. Androgens or epsilon

aminocaproic acid (EACA) may be used on a daily basis for chronic long-term prophylaxis. Short-term prophylaxis might be needed for surgery or after trauma. The administration of fresh frozen plasma to replace the missing C1 inhibitor is useful in these situations. Since there are no specific treatments in the United States available for acute attacks, patients are usually managed with supportive care. Berinert P and Cinryze are both C1 inhibitor replacement therapies and are designated as orphan drugs.

Berinert P was studied in a double-blind, placebo-controlled trial that compared two doses of Berinert P to a placebo in patients experiencing acute, moderate or severe abdominal or facial attacks. The endpoints of the study, time to onset of symptom relief and proportion of patients with worsening clinical symptoms, were found to be significantly lower in the group treated with 20 units/kg of Berinert P than in the placebo group. Based on these results, CSL Behring, its manufacturer, filed a biologic license application (BLA) for the treatment of acute attacks in patients with HAE in March 2008. A response to the BLA is expected January 2009.

The manufacturer of Cinryze, Lev Pharmaceuticals, conducted phase III trials for both the treatment and prevention of HAE attacks. The primary endpoint was achieved in each trial, demonstrating a clinically and statistically significant reduction in the time to sustained relief of acute HAE symptoms and in the number of HAE attacks. A BLA for the acute treatment of HAE was filed in July 2007. The BLA was then amended in October 2007 to include data on the prophylactic treatment of HAE. The FDA issued a complete response letter in January 2008 and requested

additional information. Lev Pharmaceuticals submitted its complete response to the letter, which the FDA accepted in May 2008. A response to the BLA is now expected in October 2008.

### Viveta (inhaled treprostinil)

An inhaled formulation of treprostinil, Viveta, has been developed and studied in patients with pulmonary arterial hypertension (PAH). An injectable formulation of treprostinil, known as Remodulin<sup>®</sup>, is currently available for subcutaneous (SC) or intravenous (IV) infusion. The injectable form is indicated for the treatment of PAH in patients with New York Heart Association (NYHA) Class II-IV symptoms.

Both forms of treprostinil are prostacyclin analogues, which are potent vasodilators. Two other prostacyclin analogues are approved in the United States for the treatment of PAH: Flolan<sup>®</sup> (epoprostenol) for infusion and Ventavis<sup>®</sup> (iloprost) for inhalation.

PAH is characterized by high blood pressure in the arteries of the lung, which can lead to heart failure and premature death. Although the exact number is unknown, PAH is thought to affect approximately 200,000 patients worldwide. Management of PAH varies depending on the severity of the disease and the patient's response to treatment.

In a clinical trial, the use of Viveta in combination with either Tracleer<sup>®</sup> (bosentan) or Revatio<sup>®</sup> (sildenafil) was compared with the use of Tracleer or Revatio alone in patients with PAH. Viveta was prepared once per day and then administered in four daily inhalation sessions, with each session lasting one to two minutes. The primary endpoint of this double-blind, placebo-controlled trial was change in six-minute walk distance (6MWD) at 12 weeks. A significant improvement in median 6MWD of approximately 20 meters was observed in the group of patients receiving Viveta in combination with Tracleer or Revatio. Based primarily on the data from this trial, United Therapeutics and Lung Rx, the manufacturers, filed a New Drug Application (NDA) in June 2008. The companies expect a response to their NDA by the end of April 2009.

### Corifollitropin alfa

Infertility is the inability of a couple to conceive after one year of regular unprotected intercourse, as defined by the American Society for Reproductive Medicine. In the United States, approximately 10 percent of all

couples experience infertility. Assisted reproductive technology (ART) can help some women become pregnant. In general, ART procedures involve surgically removing eggs from a woman's ovaries, combining them with sperm in the laboratory and then returning them to the woman's body.

Corifollitropin alfa is an investigational agent classified as a sustained follicle stimulant. It has a longer half-life than currently available follicle stimulating hormones (FSH) so that one single injection may replace the first seven injections with conventional FSH. Approved FSH products in the United States include: Bravelle<sup>®</sup> (urofollitropin), Follistim<sup>®</sup> AQ (follitropin beta) and Gonal-f<sup>®</sup> RFF (follitropin alfa). This investigational agent is a potential treatment to be used in controlled ovarian stimulation for the development of multiple follicles and pregnancy in women participating in an ART program.

Recently, Schering-Plough, the manufacturer of corifollitropin alfa, announced the results from ENGAGE, a phase III double-blind trial. In this study, a single dose of corifollitropin alfa (150 mcg) was compared with seven daily doses of follitropin beta (200 IU per day). All patients were scheduled to receive 0.25 mg gonadotropin-releasing hormone antagonist daily from stimulation day five and daily doses of follitropin beta from stimulation day eight, up to the day of triggering final oocyte maturation. The primary endpoint of this non-inferiority trial, ongoing pregnancy rate, was met with a rate of 38.9 percent in the corifollitropin alfa group and 38.1 percent in the follitropin beta group.

## Medications Recently Approved

| Manufacturer/<br>Drug Name                                      | Indication  | Mechanism of<br>Action/Drug Class   | Route of<br>Administration | Approval<br>Date | Comments   |
|---|---|---|----------------------------|------------------|--|
| <b>Hepatitis</b>  |   |   |                            |                  |  |
| Gilead Sciences/<br>Viread®<br>(tenofovir)                      | For the treatment of chronic hepatitis B in adults                            | Inhibits the formation of viral DNA/ Nucleotide reverse transcriptase inhibitor | Oral                       | 08/11/08         | Previously approved for the treatment of HIV-1 infection in combination with other antiretroviral agents.                      |
| <b>Oncology</b>   |   |   |                            |                  |  |
| Millennium Pharmaceuticals and J&J/<br>Velcade®<br>(bortezomib) | For the treatment of patients with previously untreated multiple myeloma (MM) | Interferes with the growth and survival of cancer cells/ Proteasome inhibitor   | IV injection               | 06/20/08         | Previously approved for the treatment of MM and mantle cell lymphoma in patients who have received at least one prior therapy. |

## Pipeline Medications in Phase III Trials

| Manufacturer/<br>Drug Name   | Indication  | Mechanism of<br>Action/Drug Class  | Route of<br>Administration | Comments  |
|--|---|--|----------------------------|---|
| <b>Amyloid A Amyloidosis</b>   |   |  |                            |   |
| BELLUS Health/<br>Kiacta™<br>(eprodisate),<br>formerly<br>Fibrillex™ | For the treatment of amyloid A amyloidosis            | Reduces amyloid protein deposition/<br>Amyloid fibrillogenesis inhibitor                                   | Oral                       | Designated as an orphan drug. NDA filed February 2006. FDA granted priority review status April 2006. First approvable letter August 2006. Second approvable letter July 2007. Based on recommendations from the FDA, a second phase III trial will be conducted to confirm treatment efficacy. This trial is expected to begin in the fourth quarter of 2008. In the meantime, BELLUS Health has withdrawn its current NDA for Kiacta. |
| <b>Blood Disorder</b>  |   |  |                            |   |
| CSL Behring/<br>Human<br>fibrinogen<br>concentrate                   | For the treatment of congenital fibrinogen deficiency | Replaces deficient fibrinogen/Factor I   | IV infusion                | Designated as an orphan drug. BLA filed July 2008. A response to the BLA is expected May 2009.  |
| GlaxoSmithKline/<br>Bosatria®<br>(mepolizumab)                       | For the treatment of hypereosinophilic syndromes      | Binds to and inactivates interleukin (IL)-5/Anti-IL-5 monoclonal antibody                                  | IV infusion                | Designated as an orphan drug. BLA filing anticipated in 2008.   |
| <b>Cystic Fibrosis</b>   |   |  |                            |   |
| Inspire Pharmaceuticals/<br>Denufosal                                | For the treatment of cystic fibrosis                  | Designed to enhance mucosal hydration and mucociliary clearance/Second generation P2Y <sub>2</sub> agonist | Inhalation                 | Designated as an orphan drug with fast track status. Second phase III study initiated February 2008. Primary endpoint achieved in first phase III trial June 2008.  |
| <b>Gaucher Disease</b>   |   |  |                            |   |
| Shire/<br>Velaglucerase<br>alfa                                      | For the treatment of type 1 Gaucher disease           | Replaces deficient glucocerebrosidase/ Enzyme replacement therapy  | IV infusion                | Worldwide enrollment completed for phase III clinical program July 2008. BLA filing anticipated in the second half of 2009.   |

## Pipeline Medications in Phase III Trials (continued)

| Manufacturer/<br>Drug Name  | Indication   | Mechanism of<br>Action/Drug Class   | Route of<br>Administration | Comments   |
|---|--|---|----------------------------|--|
| <b>Hepatitis</b>  |  |   |                            |  |
| Human Genome Sciences and Novartis/<br>Albupheron®<br>(albinterferon alfa-2b) | In combination with ribavirin for the treatment of chronic hepatitis C virus (HCV) infection   | Inhibits viral replication/Interferon   | Injection                  | Phase III data expected by spring 2009 and BLA filing anticipated by fall 2009.  |
| Valeant Pharmaceuticals/<br>Viramidine®<br>(taribavirin)                      | For the treatment of chronic HCV infection in combination with pegylated interferon alfa-2b  | Reduces virus synthesis/Antiviral (synthetic nucleoside analogue)   | Oral                       | Prodrug of ribavirin. Enrollment for a phase II trial using a weight-based dose of Viramidine initiated March 2007. Based on an early review of this study, Valeant will decide whether to begin a third phase III study at the weight-based dose.   |
| <b>Hereditary Angioedema</b>  |  |   |                            |  |
| CSL Behring/<br>Berinert® P<br>(C1 inhibitor)                                 | For the treatment of acute attacks in patients with HAE  | Replaces deficient C1 inhibitor/C1 inhibitor replacement therapy  | IV                         | Designated as an orphan drug. BLA filed March 2008. A response to the BLA is expected January 2009.  |
| Lev Pharmaceuticals/<br>Cinryze™<br>(C1 inhibitor)                            | For acute and prophylactic treatment of HAE attacks  | Replaces deficient C1 inhibitor/C1 inhibitor replacement therapy  | IV                         | Designated as an orphan drug. BLA for acute treatment filed July 2007. FDA granted priority review status and BLA amended to include prophylactic treatment October 2007. Complete response letter January 2008. FDA accepted complete response submission May 2008. A response to the BLA is expected October 2008. |
| <b>Human Immunodeficiency Virus (HIV)</b>                                     |  |   |                            |  |
| Schering-Plough/<br>Vicriviroc  | For the treatment of R5-type HIV infection in combination with other antiretroviral agents (which must include a protease inhibitor) in treatment-experienced patients | Inhibits entry of virus into human CD4 T-cells/Cellular chemokine receptor antagonist (CCR-5)                       | Oral                       | Initiated two large phase III trials September 2007.   |
| <b>Immune Thrombocytopenic Purpura</b>  |  |   |                            |  |
| Amgen/<br>Nplate™<br>(romiplostim)  | For the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenic purpura (ITP)   | Stimulates the thrombopoietin receptor, which helps maintain platelet levels/<br>Thrombopoiesis-stimulating protein | SC injection               | Designated as an orphan drug with fast track status. BLA filed October 2007. FDA granted priority review status January 2008. A response to the BLA was expected July 2008; however, the FDA notified Amgen that they will not issue a decision by this deadline. The timing of the FDA's response is unknown.       |

## Pipeline Medications in Phase III Trials (continued)

| Manufacturer/<br>Drug Name                              | Indication  | Mechanism of<br>Action/Drug Class  | Route of<br>Administration | Comments  |
|---|---|--|----------------------------|---|
| <b>Immune Thrombocytopenic Purpura</b>                  |   |  |                            |   |
| GlaxoSmithKline/<br>Promacta®<br>(eltrombopag)          | For the short-term treatment of previously treated patients with chronic ITP to increase platelet counts and reduce or prevent bleeding | Stimulates the proliferation and differentiation of megakaryocytes (bone marrow cells which give rise to platelets)/ Thrombopoietin-receptor agonist | Oral                       | NDA filed December 2007. FDA granted priority review status March 2008. A response to the NDA was expected June 2008; however, the FDA notified GlaxoSmithKline that they require more time to review the application. A response is now expected September 2008. |
| <b>Infertility</b>                                      |   |  |                            |   |
| Schering-Plough/<br>Corifollitropin alfa                | For the development of multiple follicles and pregnancy in women participating in an ART program  | Stimulates ovarian follicular growth/ Sustained follicle stimulant   | SC injection               | Primary endpoints in phase III trial were met July 2008.  |
| <b>Inflammatory Diseases</b>                            |   |  |                            |   |
| Centocor and Schering-Plough/<br>Golimumab              | For the treatment of rheumatoid arthritis (RA), psoriatic arthritis and ankylosing spondylitis  | Targets tumor necrosis factor (TNF) alpha, which is involved in the inflammatory process/ TNF inhibitor  | SC injection               | BLA filed June 2008. A response to the BLA is expected April 2009.  |
| Centocor/<br>Ustekinumab                                | For the treatment of adult patients with chronic moderate to severe plaque psoriasis  | Targets IL-12 and IL-23/ Dual IL inhibitor   | SC injection               | BLA filed December 2007. In August 2008, the FDA extended the review of the BLA to December 2008 to provide additional time for review of amendments provided by Centocor.  |
| Novartis/<br>ACZ885                                     | For the treatment of Muckle-Wells syndrome  | Targets IL-1β/ IL-1β inhibitor   | SC injection               | Designated as an orphan drug. BLA filing planned for 2009.  |
| Roche and Chugai/<br>Actemra™<br>(tocilizumab)          | For reducing the signs and symptoms in adults with moderate to severe RA  | Blocks IL-6 receptors/Monoclonal antibody  | IV infusion                | BLA filed November 2007. A response to the BLA is expected September 2008.  |
| <b>Multiple Sclerosis</b>                               |   |  |                            |   |
| Eli Lilly and BioMS Medical/<br>Dirucotide<br>(MBP8298) | For the treatment of secondary progressive multiple sclerosis (MS)  | Induction or restoration of immunological tolerance/Synthetic human myelin basic protein   | IV infusion                | Patient recruitment for phase III trial completed August 2008.  |
| Novartis/<br>Fingolimod,<br>formerly FTY720             | For the treatment of relapsing-remitting MS   | Reduces inflammation and myelin damage in the brain and spinal cord/ Immunomodulatory agent  | Oral                       | NDA filing planned for the end of 2009.   |
| Sanofi-aventis/<br>Teriflunomide                        | For the treatment of relapsing forms of MS  | Inhibits pyrimidine synthesis/ Immunomodulatory agent  | Oral                       | Also being studied in combination with interferon-beta and with Copaxone® (glatiramer acetate).   |

## Pipeline Medications in Phase III Trials (continued)

| Manufacturer/<br>Drug Name   | Indication   | Mechanism of<br>Action/Drug Class   | Route of<br>Administration   | Comments   |
|--|--|---|------------------------------|--|
| <b>Neuroendocrine Disorders</b>  |  |   |                              |  |
| Novartis/<br>Pasireotide   | For the treatment of Cushing's disease and acromegaly  | Binds somatostatin receptors/<br>Somatostatin analogue  | SC injection                 | NDA filing for Cushing's disease now expected in 2010 (previously planned for 2009).   |
| <b>Oncology</b>  |  |   |                              |  |
| AstraZeneca/<br>Zactima®<br>(vandetanib)   | For the second-line treatment of non-small cell lung cancer (NSCLC)                              | Reduces tumor cell growth and blood supply/Multikinase inhibitor  | Oral                         | NDA filing now expected in the first half of 2009 (previously planned for 2008).   |
| Cell Therapeutics/<br>Opaxio™<br>(paclitaxel poliglumex),<br>formerly<br>Xyotax™ | For the treatment of advanced NSCLC in women   | Promotes assembly and stabilizes microtubules resulting in inhibition of cellular division/<br>Antimicrotubule chemotherapy agent | IV infusion                  | Links paclitaxel to a biodegradable polyglutamate polymer that delivers more chemotherapy to tumor cells. Received Special Protocol Assessment (SPA) approval from the FDA for phase III trial September 2007. FDA granted fast track status.  |
| Celtic Pharma and Neurobiological Technologies/<br>Xerecept®<br>(corticotropin)  | For the treatment of peritumoral brain edema   | Reduces edema/<br>Synthetic human corticotropin releasing factor  | SC injection                 | Designated as an orphan drug. NDA filing planned for 2008.   |
| Cephalon/<br>Lestaurtinib  | For the treatment of acute myeloid leukemia  | Inhibits FMS-like tyrosine kinase-3 (FLT3) mutations/FLT3 inhibitor   | Oral                         | Designated as an orphan drug. NDA filing now expected in 2009 (previously planned for first half of 2008).   |
| Dendreon/<br>Provenge®<br>(sipuleucel-T)   | For the treatment of metastatic hormone-refractory prostate cancer (HRPC)                        | Stimulates immune system to target and destroy cancer cells/Active cellular immunotherapy   | IV infusion                  | BLA filed November 2006. Complete response letter May 2007. The FDA will accept either a positive interim or final analysis of survival from the ongoing phase III trial to amend the BLA. Dendreon expects the Independent Data Monitoring Committee to review the interim analysis of overall survival October 2008. |
| Genmab and GlaxoSmithKline/<br>HuMax-CD20®<br>(ofatumumab)                       | For the treatment of refractory chronic lymphocytic leukemia (CLL)                               | Targets the binding site of CD20 on B cells/<br>Anti-CD20 monoclonal antibody   | IV infusion                  | Potential BLA filing in 2008.  |
| Genta/<br>Genasense®<br>(oblimersen)   | For the treatment of relapsed or refractory CLL in combination with chemotherapy                 | Inhibits the production of Bcl-2/Antisense therapy  | IV infusion                  | NDA filed December 2005. Non-approvable letter December 2006. NDA amended June 2008. A response to the NDA is expected December 2008.  |
| Lorus Therapeutics and Zor Pharmaceuticals/<br>Virulizin®                        | For first-line treatment of advanced pancreatic cancer in combination with Gemzar® (gemcitabine) | Increases the cytogenic effects of macrophages/<br>Biologic response modifier   | Intramuscular (IM) injection | Rolling NDA accepted July 2005. Designated as an orphan drug with fast track status.   |

## Pipeline Medications in Phase III Trials (continued)

| Manufacturer/<br>Drug Name  | Indication   | Mechanism of<br>Action/Drug Class   | Route of<br>Administration | Comments  |
|---|--|---|----------------------------|---|
| <b>Oncology</b>   |  |   |                            |   |
| Marshall<br>Edwards/<br>Phenoxodiol   | For the treatment of<br>HRPC in Taxotere®<br>(docetaxel)<br>nonresponders<br>and recurrent<br>chemotherapy-<br>resistant, late-stage<br>ovarian cancer | Causes cell death<br>through inhibition of<br>antiapoptotic proteins/<br>Antineoplastic<br>(multiple signal<br>transduction<br>regulator)     | IV injection/Oral          | Received SPA approval from the FDA<br>for phase III trial in ovarian cancer.<br>FDA granted fast track status.  |
| Novartis/<br>Everolimus<br>(RAD001)   | For the treatment of<br>advanced renal cell<br>carcinoma (RCC) and<br>neuroendocrine<br>tumors   | Inhibits tumor cell<br>growth and the<br>formation of new<br>blood vessels/<br>Antineoplastic<br>(mammalian target of<br>rapamycin inhibitor) | Oral                       | NDA filing for RCC planned for the<br>second half of 2008.  |
| Protherics PLC/<br>Voraxaze™<br>(glucarpidase),<br>formerly<br>Carboxy-<br>peptidase G2 | Adjunctive therapy for<br>cancer patients<br>undergoing<br>chemotherapy who<br>are at risk for<br>methotrexate (MTX)<br>toxicity                       | Rapidly reduces<br>serum MTX<br>levels/Recombinant<br>enzyme  | IV injection               | Designated as an orphan drug with fast<br>track status.<br>BLA originally filed September 2006 and<br>resubmitted November 2006.<br>FDA requested additional information,<br>and agreed to let Protherics resubmit its<br>BLA as a rolling submission. Protherics<br>plans to begin submitting a rolling BLA in<br>the second half of 2008.<br>Available through an expanded access<br>program. |
| Sanofi-aventis<br>and Regeneron/<br>Aflibercept   | For the third-line<br>treatment of ovarian<br>cancer   | Binds to circulating<br>vascular endothelial<br>growth factor<br>(VEGF)/Anti-<br>angiogenesis agent   | IV infusion                | Phase II study did not achieve primary<br>endpoint. The companies are evaluating<br>the data in order to determine the next<br>steps.   |
| Sanofi-aventis/<br>Larotaxel  | For second-line<br>treatment of<br>pancreatic cancer   | Inhibits the growth<br>and development of<br>cancer cells/Taxane<br>derivative  | IV infusion                | NDA filing planned for fourth quarter<br>2009.  |
| <b>Osteoporosis</b>   |  |   |                            |   |
| Amgen/<br>Denosumab   | For the treatment of<br>postmenopausal<br>osteoporosis (PMO)<br>and treatment-induced<br>bone loss   | Inhibits<br>bone destruction/<br>Monoclonal antibody  | SC injection               | All endpoints were met in the phase III<br>trial for treatment-induced bone loss.<br>Primary endpoint was achieved in phase<br>III study for PMO. Amgen plans to<br>present the complete data set in<br>September 2008.   |
| <b>Pulmonary Arterial Hypertension</b>  |  |   |                            |   |
| Pfizer/<br>Thelin™<br>(sitaxsentan)   | For the treatment of<br>PAH  | Reduces vascular<br>smooth muscle<br>constriction/<br>Endothelin receptor<br>antagonist   | Oral                       | Designated as an orphan drug.<br>NDA filed May 2005.<br>First approvable letter March 2006.<br>Second approvable letter July 2006.<br>Third approvable letter June 2007.<br>Pfizer plans to begin an additional phase<br>III study during the second half of 2008.  |

## Pipeline Medications in Phase III Trials (continued)

| Manufacturer/<br>Drug Name                            | Indication   | Mechanism of<br>Action/Drug Class  | Route of<br>Administration | Comments  |
|---|--|--|----------------------------|---|
| <b>Respiratory Syncytial Virus</b>                    |  |  |                            |   |
| MedImmune and AstraZeneca/<br>Numax®<br>(motavizumab) | For the prevention of respiratory syncytial virus (RSV) infection in high-risk pediatric populations | Inhibits RSV replication/<br>Monoclonal antibody   | IM injection               | Expected to be more potent than Synagis® (palivizumab), which is the current standard of care for the prevention of RSV.<br>BLA filed January 2008.<br>A response to the BLA is expected November 2008.   |
| <b>Transplant</b>                                     |  |  |                            |   |
| Novartis/<br>Certican™<br>(everolimus)                | For the prevention of solid organ transplant rejection in combination with Neoral® (cyclosporine)    | Inhibits T-cell proliferation, which are cells involved in the rejection process/<br>Immunosuppressant (mammalian target of rapamycin inhibitor) | Oral                       | NDA filed December 2002.<br>First approvable letter October 2003.<br>Second approvable letter August 2004.<br>FDA Advisory Committee recommended that additional study data be provided to support the NDA November 2005.<br>Clinical trials are ongoing. |

## New Dosage Forms in the Pipeline

| Manufacturer/<br>Drug Name                         | Indication  | Mechanism of<br>Action/Drug Class                                | Current<br>Route of<br>Administration | Investigational<br>Route of<br>Administration* | Comments  |
|--|---|--|---------------------------------------|--|---|
| <b>Cystic Fibrosis</b>                             |   |  |                                       |  |   |
| Gilead Sciences/<br>Cayston™<br>(aztreonam lysine) | For the treatment of patients with cystic fibrosis who have pulmonary <i>Pseudomonas aeruginosa</i> | Inhibits bacterial cell wall synthesis/<br>Monobactam antibiotic | IV injection                          | Inhalation                                     | Designated as an orphan drug.<br>NDA filed November 2007.<br>A response to the NDA is expected September 2008.<br>Available through an expanded access program. |
| Novartis/<br>TBM100<br>(tobramycin)                | For the treatment of patients with cystic fibrosis who have pulmonary <i>Pseudomonas aeruginosa</i> | Disrupts protein synthesis/<br>Aminoglycoside antibiotic         | Solution for inhalation               | Powder for inhalation                          | Expected to provide more rapid and convenient administration of tobramycin.<br>NDA filing planned for 2009.   |

## New Dosage Forms in the Pipeline (continued)

| Manufacturer/<br>Drug Name   | Indication  | Mechanism of<br>Action/Drug Class  | Current<br>Route of<br>Administration | Investigational<br>Route of<br>Administration* | Comments  |
|--|---|--|---------------------------------------|--|---|
| <b>Multiple Sclerosis</b>  |   |  |                                       |  |   |
| Merck Serono<br>and Teva/<br>Mylinax®<br>(cladribine)              | For the<br>treatment<br>of relapsing<br>forms of MS | Interferes with<br>lymphocytes, which<br>are involved in the<br>pathology of MS/<br>Antineoplastic (purine<br>nucleoside analogue) | IV infusion                           | Oral   | FDA granted fast track<br>status.<br>Full enrollment for phase<br>III study completed<br>January 2007. Expected<br>study completion<br>November 2008. |
| <b>Pulmonary Arterial Hypertension</b>                             |   |  |                                       |  |   |
| United<br>Therapeutics and<br>Lung Rx/<br>Viveta<br>(treprostinil) | For the<br>treatment of<br>PAH                      | Dilates pulmonary<br>blood vessels/<br>Prostacyclin<br>analogue  | SC or IV infusion                     | Inhalation                                     | Studied in combination<br>with Tracleer (bosentan)<br>or Revatio (sildenafil).<br>NDA filed June 2008.  |

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

## New Indications in the Pipeline

| Manufacturer/<br>Drug Name   | Current Indication   | Investigational<br>Indication   | Mechanism of<br>Action/Drug Class   | Route of<br>Administration | Comments   |
|--|--|---|---|----------------------------|--|
| <b>Hepatitis</b>   |  |   |   |                            |  |
| Three Rivers<br>Pharmaceuticals/<br>Infergen®<br>(interferon<br>alfacon-1) | For the treatment<br>of HCV infection  | For the treatment of<br>chronic HCV in<br>combination with<br>ribavirin after failure<br>to respond to<br>previous course of<br>pegylated interferon<br>plus ribavirin                            | Inhibits viral<br>replication/Interferon  | SC injection               | Clinical trials<br>are ongoing.  |
| <b>Inflammatory Diseases</b>   |  |   |   |                            |  |
| Genentech and<br>Biogen Idec/<br>Rituxan®<br>(rituximab)                   | For the treatment<br>of non-Hodgkin's<br>lymphoma (NHL)<br><br>For the treatment of<br>moderately to<br>severely active RA<br>in patients who<br>have had an<br>inadequate<br>response to one<br>or more TNF<br>inhibitors | For the treatment of<br>moderately to<br>severely active RA<br>in biologic-naïve<br>patients (patients<br>who have not<br>received a biologic<br>medication for<br>the treatment of<br>RA before) | Reduces the amount<br>of CD20-positive<br>B-cells in the<br>blood/Therapeutic<br>antibody | IV infusion                | The primary<br>endpoint of the<br>phase III trial was<br>met January 2008. |

## New Indications in the Pipeline (continued)

| Manufacturer/<br>Drug Name                                       | Current Indication  | Investigational<br>Indication   | Mechanism of<br>Action/Drug Class   | Route of<br>Administration | Comments   |
|--|---|---|---|----------------------------|--|
| <b>Inflammatory Diseases</b>                                     |   |   |   |                            |  |
| UCB/<br>Cimzia®<br>(certolizumab<br>pegol)                       | For the treatment of<br>Crohn's disease   | For the treatment<br>of moderate to<br>severe or active<br>RA and<br>moderate to<br>severe psoriasis  | Targets TNF alpha,<br>which is involved in<br>the inflammatory<br>process/ TNF<br>inhibitor     | SC injection               | BLA for the<br>treatment of RA filed<br>December 2007.<br>UCB is evaluating further<br>development or<br>alternatives in psoriasis.  |
| <b>Oncology</b>  |   |   |   |                            |  |
| Cephalon/<br>Treanda®<br>(bendamustine)                          | For the treatment of<br>CLL   | For the treatment<br>of NHL in<br>patients who<br>failed Rituxan®<br>(rituximab)  | Causes cell death<br>and disrupts cell<br>division/ Hybrid<br>alkylating agent                  | IV infusion                | NDA filed December<br>2007.<br>A response to the NDA is<br>expected October 2008.  |
| Genentech/<br>Avastin®<br>(bevacizumab)                          | For the treatment of<br>breast cancer,<br>colorectal cancer<br>and NSCLC  | For the first-line<br>treatment of<br>RCC and<br>relapsed<br>glioblastoma<br>multiforme   | Binds to and<br>inhibits the biologic<br>activity of human<br>VEGF/ Anti-<br>angiogenesis agent | IV infusion                | sBLA filings planned for<br>2008.  |
| Novartis/<br>Tasigna®<br>(nilotinib)                             | For the treatment of<br>chronic and<br>accelerated phase<br>Philadelphia<br>chromosome<br>positive chronic<br>myelogenous<br>leukemia | For the treatment<br>of<br>gastrointestinal<br>stromal tumor in<br>patients who<br>have failed both<br>Gleevec®<br>(imatinib) and<br>Sutent®<br>(sunitinib) | Inhibits Bcr-Abl<br>kinase/Tyrosine<br>kinase inhibitor   | Oral                       | sNDA filing anticipated in<br>2009.  |
| Pfizer/<br>Sutent®<br>(sunitinib)                                | For the treatment of<br>gastrointestinal<br>stromal tumor and<br>advanced RCC   | For the<br>treatment of<br>colorectal<br>cancer,<br>metastatic breast<br>cancer and<br>NSCLC  | Reduces tumor cell<br>growth and blood<br>supply/Multikinase<br>inhibitor                       | Oral                       | Phase III trials ongoing.  |
| Schering-<br>Plough/<br>PegIntron™<br>(peginterferon<br>alfa-2b) | For the treatment of<br>chronic HCV<br>infection  | For the adjuvant<br>treatment of<br>stage III<br>melanoma   | Unknown<br>mechanism<br>of action in cancer<br>treatment/Interferon                             | SC injection               | sBLA accepted and<br>granted priority review<br>status January 2008.<br>FDA Advisory Committee<br>postponed a planned<br>review of the sBLA and<br>requested clarification of<br>existing data in March<br>2008. No new review date<br>has been set. |

## New Indications in the Pipeline (continued)

| Manufacturer/<br>Drug Name                 | Current Indication  | Investigational<br>Indication                                  | Mechanism of<br>Action/Drug Class                              | Route of<br>Administration | Comments  |
|--|---|--|--|----------------------------|---|
| <b>Osteoporosis</b>                        |   |  |  |                            |   |
| Eli Lilly/<br>Forteo®<br>(teriparatide)    | For the treatment of men and postmenopausal women with osteoporosis who are at high risk for fracture | For the treatment of glucocorticoid-induced osteoporosis (GIO) | Stimulates bone formation/<br>Parathyroid hormone analogue     | SC injection               | sNDA filed February 2007. Eli Lilly reported receiving an approvable letter April 2008. |
| Novartis/<br>Reclast®<br>(zoledronic acid) | For the treatment of Paget's disease and PMO  | For the treatment of GIO                                       | Inhibits osteoclast-mediated bone resorption/IV bisphosphonate | IV infusion                | sNDA filed 2008.  |

## Glossary of Terms

**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. Effective August 11, 2008, a complete response letter will be issued to the applicant in place of an approvable letter.

**BLA** – stands for “Biologic 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.

**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.

**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.

**Non-approvable 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. Effective August 11, 2008, a complete response letter will be issued to the applicant in place of a non-approvable letter.

**Non-inferiority trial** – intended to show that the effect of a new treatment is not worse than that of standard treatment by more than a specified amount or margin.

**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.

**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.

**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 Biologic 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.

## References

### Manufacturers' web sites

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[www.biopharminsight.com](http://www.biopharminsight.com)

Centers for Disease Control and  
Prevention  
[www.cdc.gov](http://www.cdc.gov)

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\*Information in the report is current as of August 2008, and was accessed on August 18, 2008.

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