



UCB
News

UCB Presents Latest Research from Immunology Portfolio at American College of Rheumatology Annual Meeting

Data presentations include:

- **Positive results from Period 1 of the C-EARLY™ Phase 3 study of CIMZIA® (certolizumab pegol) combined with optimized methotrexate treatment in DMARD-naïve, recently diagnosed, adult rheumatoid arthritis patients with moderate-to-severe disease activity and poor prognostic factors**
- **Long term efficacy and safety data reinforcing the clinical profile of CIMZIA® in patients with moderate-to-severe rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis**
- **Three new studies on investigational treatments for systemic lupus erythematosus and Sjögren's Syndrome**

Atlanta (US) – November 6, 2015 – UCB, a global biopharmaceutical company focusing on immunology and neurology treatment and research, is presenting 19 studies of CIMZIA® (certolizumab pegol) and investigational medicines for systemic lupus erythematosus (SLE) and Sjögren's Syndrome at the American College of Rheumatology (ACR) 2015 Annual Scientific Meeting, being held in San Francisco, CA from November 6-11.

“The CIMZIA® studies contribute to the clinical understanding of this established therapy and will help rheumatologists make the most informed treatment decisions for their patients. Notably, findings from Period 1 of the C-EARLY™ study demonstrated the importance of identifying RA patients with poor prognostic factors, who may benefit from combination therapy following diagnosis, providing an important option for a long-term treatment strategy for people living with RA. Evidence suggests that early assessment, recognition and treatment of RA symptoms are associated with less joint destruction in the long-term and higher chances of achieving DMARD-free disease remission and optimal outcomes,” said Emmanuel Caeymaex, Head, Immunology Patient Value Unit, UCB. “In addition, the data on UCB's investigational compounds provide important insights into their potential role in treating other immunological diseases.”

In the US, CIMZIA® is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis, for the treatment of adults with active psoriatic arthritis (PsA) and for adults with active ankylosing spondylitis (AS).¹ In addition, it is indicated for reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.¹ See important safety information including risk of serious infections and tuberculosis below.

Following is a guide to the UCB-sponsored data presentations:

CIMZIA® RA, Safety & Women of Child-bearing Age (6 abstracts)

New – [Oral] Certolizumab Pegol in Combination with Methotrexate in DMARD-Naïve Patients with Active, Severe, Progressive Rheumatoid Arthritis: Results from a Randomized, Double-Blind, Controlled Phase 3 Study

- Session: Rheumatoid Arthritis-Small Molecules, Biologics and Gene Therapy Poster I: Biologics
- Session date: Sunday, November 8
- Session time: 2:30 – 4:00 p.m.
- Abstract: 968

New – Early Response As a Predictor of Long-Term Remission in DMARD-Naïve Patients with Severe, Active and Progressive Rheumatoid Arthritis Treated with Certolizumab Pegol in Combination with Methotrexate

- Session: Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy Poster II
- Session date: Monday, November 9
- Session time: 8:30 a.m. – 4:00 p.m., Presentation time: 9:00 – 11:00 a.m.
- Abstract: 1638

New – Reduction of Disease Burden on Workplace and Household Productivity Following 52 Weeks of Treatment with Certolizumab Pegol in Combination with Methotrexate in DMARD-Naïve Patients with Active, Severe, Progressive Rheumatoid Arthritis

- Session: Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy Poster II
- Session date: Tuesday, November 10
- Session time: 8:30 a.m. – 4:00 p.m., Presentation time: 9:00 – 11:00 a.m.
- Abstract: 2736

New – Clinical Benefit of 1-year Certolizumab Pegol Treatment in MTX-naïve, Early Rheumatoid Arthritis Patients Is Maintained after Discontinuation up to 1 Year

- Session: Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy Poster II
- Session date: Monday, November 9
- Session time: 8:30 a.m. – 4:00 p.m., Presentation time: 9:00 – 11:00 a.m.
- Abstract: 1636

New – Improvement in Disease Activity and the Long-Term Risk of Serious Infectious Events in Rheumatoid Arthritis Patients Treated with Certolizumab Pegol

- Session: Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy Poster II
- Session date: Sunday, November 8
- Session time: 8:30 a.m. – 4:00 p.m., Presentation time: 9:00 – 11:00 a.m.
- Abstract: 561

New – Characteristics and Outcomes of Prospectively-Reported Pregnancies Exposed to Certolizumab Pegol from a Safety Database

- Session: Reproductive Issues in Rheumatic Disorders: Basic and Clinical Aspects

- Session date: Tuesday, November 10
- Session time: 8:30 a.m. – 4:00 p.m., Presentation time: 9:00 – 11:00 a.m.
- Abstract: 2523

CIMZIA® PsA (3 abstracts)

Previously presented at EADV 2015 – Associations Between Skin Outcomes By Body Area Affected and Health-Related Quality of Life in Patients with Psoriatic Arthritis Treated with Certolizumab Pegol

- Session: Spondyloarthropathies and Psoriatic Arthritis - Clinical Aspects and Assessments Poster I
- Session date: Sunday, November 8
- Session time: 8:30 a.m. – 4:00 p.m., Presentation time: 9:00 – 11:00 a.m.
- Abstract: 654

New – Long-Term Improvements with Certolizumab Pegol in Joints and Extra-Articular Manifestations of Psoriatic Arthritis in Patients with and without Prior Anti-TNF Exposure

- Session: Spondyloarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment Poster III: Therapy
- Session date: Tuesday, November 10
- Session time: 8:30 a.m. – 4:00 p.m., Presentation time: 9:00 – 11:00 a.m.
- Abstract: 2835

Previously presented at EULAR 2015 – Clinical Responses in Joint and Skin Outcomes and Patient-Reported Outcomes Are Associated with Increased Productivity in the Workplace and at Home in Psoriatic Arthritis Patients Treated with Certolizumab Pegol

- Session: Spondyloarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment Poster III: Therapy
- Session date: Tuesday, November 10
- Session time: 8:30 a.m. – 4:00 p.m., Presentation time: 9:00 – 11:00 a.m.
- Abstract: 2860

General Rheumatic Presentations (2 abstracts)

Previously presented at EULAR 2015 – The Most Frequent Fears and Beliefs of 226 Patients with Rheumatoid Arthritis or Spondyloarthritis, Using a Novel Questionnaire

- Session: Rheumatoid Arthritis - Clinical Aspects Poster III: Biomarkers, PROs, and Measurements of Disease Activity
- Session date: Tuesday, November 10
- Session time: 8:30 a.m. – 4:00 p.m., Presentation time: 9:00 – 11:00 a.m.
- Abstract: 2629

Previously presented at EULAR 2015 – Development and Validation of a Questionnaire Assessing the Fears and Beliefs of Patients Suffering from Chronic Rheumatic Diseases

- Session: Rheumatoid Arthritis - Clinical Aspects Poster III: Biomarkers, PROs, and

Measurements of Disease Activity

- Session date: Tuesday, November 10
- Session time: 8:30 a.m. – 4:00 p.m., Presentation time: 9:00 – 11:00 a.m.
- Abstract: 2632

Presentations on Investigational Studies of Certolizumab Pegol in Axial Spondyloarthritis (3 abstracts)

New – Discrepancies between Patients and Physicians Acceptable Symptomatic States in Axial Spondyloarthritis: Findings from the RAPID-axSpA study

- Session: Spondyloarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment Poster III: Therapy
- Session date: Tuesday, November 10
- Session time: 8:30 a.m. – 4:00 p.m., Presentation time: 9:00 – 11:00 a.m.
- Abstract: 671

New – Effect of Weight on Efficacy of Certolizumab Pegol in Patients with Axial Spondyloarthritis

- Session: Spondyloarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment Poster III: Therapy
- Session date: Tuesday, November 10
- Session time: 8:30 a.m. – 4:00 p.m., Presentation time: 9:00 – 11:00 a.m.
- Abstract: 2859

Previously presented at EULAR 2015 – Clinical Responses and Improvements in Patient-Reported Outcomes are Associated with Increased Productivity in the Workplace and at Home in Axial Spondyloarthritis Patients Treated with Certolizumab Pegol

- Session: Spondyloarthropathies and Psoriatic Arthritis - Clinical Aspects and Assessments Poster I
- Session date: Sunday, November 8
- Session time: 8:30 – 4:00 p.m., Presentation time: 9:00 – 11:00 a.m.
- Abstract: 653

Investigational Medicines (5 abstracts)

New (Research Collaboration) – Inhibition of B Cell Activation and Plasma Cell Differentiation by Epratuzumab, a Humanized Monoclonal Antibody Targeting CD22

- Session: B cell Biology and Targets in SLE, pSS, and other Autoimmune Disease Poster II
- Session date: Monday, November 9
- Session time: 8:30 a.m. – 4:00 p.m., Presentation time: 9:00 – 11:00 a.m.
- Abstract: 1107

New (Research Collaboration) – Epratuzumab, a Monoclonal Antibody Targeting CD22 on B Cells, Stimulates the Phosphorylation of Upstream Inhibitory Signals of the B Cell Receptor

- Session: B cell Biology and Targets in SLE, pSS, and other Autoimmune Disease
- Session date: Monday, November 9

- Session time: 08:30 a.m. – 4:00 p.m., Presentation time: 9:00 – 11:00 a.m.
- Abstract: 1108

New – [Oral] Efficacy and safety of epratuzumab in patients with moderate-to-severe systemic lupus erythematosus: results from two phase 3, randomized, placebo-controlled trials

- Session: ACR Late-breaking Abstract Session
- Session date: Tuesday, November 10
- Session time: 4:30 – 6:00 p.m.
- Abstract: 4L

New – Repeated Administration of Dapirolizumab Pegol (DZP) Appears Safe and Well Tolerated in Patients with Systemic Lupus Erythematosus (SLE) and Is Accompanied By an Improvement in Disease Activity: Results from a Phase 1 Study

- Session: Systemic Lupus Erythematosus - Clinical Aspects and Treatment VI: Novel Therapies
- Session date: Tuesday, November 10
- Session time: 4:30 – 6:00 p.m.
- Abstract: 3222

New (Research Collaboration) – Phosphatidylinositol-3-Kinase Delta Pathway a Novel Therapeutic Target for Sjögren's Syndrome

- Session: Sjögren's Syndrome I: Basic Insights
- Session date: Sunday, November 8
- Session time: 4:30 – 6:00 p.m.
- Abstract: 1053

Investigational Compounds

Epratuzumab is licensed from Immunomedics Inc. and is not approved for the treatment of SLE by any regulatory authority worldwide.

Dapirolizumab pegol (CDP7657), an anti-CD40L pegylated Fab being developed in systemic lupus erythematosus (SLE) jointly with Biogen, completed a clinical Phase 1b study at the end of 2014. The compound is scheduled to progress to Phase 2 in 2016 and is not approved by any regulatory authority worldwide.

UCB5857 is an investigational medicine for the treatment of immune-inflammatory diseases and is not approved by any regulatory authority worldwide.

About CIMZIA®

CIMZIA® is the only Fc-free, PEGylated anti-TNF (Tumor Necrosis Factor). CIMZIA® has a high affinity for human TNF-alpha, selectively neutralizing the pathophysiological effects of TNF-alpha.

CIMZIA® is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis. In addition, it is indicated for reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate

response to conventional therapy, for the treatment of adults with active psoriatic arthritis (PsA) and for adults with active ankylosing spondylitis (AS). See important safety information including risk of serious bacterial, viral and fungal infections and tuberculosis below.

Important Safety Information about CIMZIA® in the US¹

Risk of Serious Infections and Malignancy

Patients treated with CIMZIA® are at an increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. CIMZIA® should be discontinued if a patient develops a serious infection or sepsis. Reported infections include:

- **Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before CIMZIA® use and during therapy. Treatment for latent infection should be initiated prior to CIMZIA® use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.**

The risks and benefits of treatment with CIMZIA® should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with CIMZIA®, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which CIMZIA® is a member. CIMZIA® is not indicated for use in pediatric patients.

Patients treated with CIMZIA® are at an increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

Treatment with CIMZIA® should not be initiated in patients with an active infection, including clinically important localized infections. CIMZIA® should be discontinued if a patient develops a serious infection or sepsis. Patients greater than 65 years of age, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants (e.g., corticosteroids or methotrexate) may be at a greater risk

of infection. Patients who develop a new infection during treatment with CIMZIA® should be closely monitored, undergo a prompt and complete diagnostic workup appropriate for immunocompromised patients, and appropriate antimicrobial therapy should be initiated. Appropriate empiric antifungal therapy should also be considered while a diagnostic workup is performed for patients who develop a serious systemic illness and reside or travel in regions where mycoses are endemic.

Malignancies

During controlled and open-labeled portions of CIMZIA® studies of Crohn's disease and other diseases, malignancies (excluding non-melanoma skin cancer) were observed at a rate of 0.5 per 100 patient-years among 4,650 CIMZIA®-treated patients versus a rate of 0.6 per 100 patient-years among 1,319 placebo-treated patients. In studies of CIMZIA® for Crohn's disease and other investigational uses, there was one case of lymphoma among 2,657 CIMZIA®-treated patients and one case of Hodgkin lymphoma among 1,319 placebo-treated patients. In CIMZIA® RA clinical trials (placebo-controlled and open label), a total of three cases of lymphoma were observed among 2,367 patients. This is approximately 2-fold higher than expected in the general population. Patients with RA, particularly those with highly active disease, are at a higher risk for the development of lymphoma. The potential role of TNF blocker therapy in the development of malignancies is not known.

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blocking agents (initiation of therapy ≤18 years of age), of which CIMZIA® is a member. Approximately half of the cases were lymphoma (including Hodgkin's and non-Hodgkin's lymphoma), while the other cases represented a variety of different malignancies and included rare malignancies associated with immunosuppression and malignancies not usually observed in children and adolescents. Most of the patients were receiving concomitant immunosuppressants.

Cases of acute and chronic leukemia have been reported with TNF-blocker use. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for developing leukemia.

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma that has a very aggressive disease course and is usually fatal, have been reported in patients treated with TNF blockers, including CIMZIA®. The majority of reported TNF blocker cases occurred in adolescent and young adult males with Crohn's disease or ulcerative colitis. Almost all of these patients had received treatment with the immunosuppressants azathioprine and/or 6-mercaptopurine (6-MP) concomitantly with a TNF blocker at or prior to diagnosis. Carefully assess the risks and benefits of treatment with CIMZIA®, especially in these patient types.

Periodic skin examinations are recommended for all patients, particularly those with risk factors for skin cancer.

Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. CIMZIA® has not been formally studied in patients with CHF. Exercise caution when using CIMZIA® in patients who have heart failure and monitor them carefully.

Hypersensitivity

Symptoms compatible with hypersensitivity reactions, including angioedema, dyspnea, hypotension, rash, serum sickness, and urticaria, have been reported rarely following CIMZIA[®] administration. Some of these reactions occurred after the first administration of CIMZIA[®]. If such reactions occur, discontinue further administration of CIMZIA[®] and institute appropriate therapy.

Hepatitis B Reactivation

Use of TNF blockers, including CIMZIA[®], has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. Some cases have been fatal. Test patients for HBV infection before initiating treatment with CIMZIA[®]. Exercise caution in prescribing CIMZIA[®] for patients identified as carriers of HBV, with careful evaluation and monitoring prior to and during treatment. In patients who develop HBV reactivation, discontinue CIMZIA[®] and initiate effective anti-viral therapy with appropriate supportive treatment.

Neurologic Reactions

Use of TNF blockers, including CIMZIA[®], has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis, and with peripheral demyelinating disease, including Guillain-Barré syndrome. Rare cases of neurological disorders, including seizure disorder, optic neuritis, and peripheral neuropathy have been reported in patients treated with CIMZIA[®]. Exercise caution in considering the use of CIMZIA[®] in patients with these disorders.

Hematologic Reactions

Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Medically significant cytopenia (e.g., leukopenia, pancytopenia, thrombocytopenia) has been infrequently reported with CIMZIA[®]. Advise all patients to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on CIMZIA[®]. Consider discontinuation of CIMZIA[®] therapy in patients with confirmed significant hematologic abnormalities.

Drug Interactions

An increased risk of serious infections has been seen in clinical trials of other TNF blocking agents used in combination with anakinra or abatacept. Formal drug interaction studies have not been performed with rituximab or natalizumab; however, because of the nature of the adverse events seen with these combinations with TNF blocker therapy, similar toxicities may also result from the use of CIMZIA[®] in these combinations. Therefore, the combination of CIMZIA[®] with anakinra, abatacept, rituximab, or natalizumab is not recommended. Interference with certain coagulation assays has been detected in patients treated with CIMZIA[®]. There is no evidence that CIMZIA[®] therapy has an effect on in vivo coagulation. CIMZIA[®] may cause erroneously elevated aPTT assay results in patients without coagulation abnormalities.

Autoimmunity

Treatment with CIMZIA[®] may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. Discontinue treatment if symptoms of lupus-like syndrome develop.

Immunizations

Do not administer live vaccines or live-attenuated vaccines concurrently with CIMZIA[®].

Adverse Reactions

In controlled Crohn's clinical trials, the most common adverse events that occurred in $\geq 5\%$ of CIMZIA[®] patients (n=620) and more frequently than with placebo (n=614) were upper respiratory infection (20% CIMZIA[®], 13% placebo), urinary tract infection (7% CIMZIA[®], 6% placebo), and arthralgia (6% CIMZIA[®], 4% placebo). The proportion of patients who discontinued treatment due to adverse reactions in the controlled clinical studies was 8% for CIMZIA[®] and 7% for placebo.

In controlled RA clinical trials, the most common adverse events that occurred in $\geq 3\%$ of patients taking CIMZIA[®] 200 mg every other week with concomitant methotrexate (n=640) and more frequently than with placebo with concomitant methotrexate (n=324) were upper respiratory tract infection (6% CIMZIA[®], 2% placebo), headache (5% CIMZIA[®], 4% placebo), hypertension (5% CIMZIA[®], 2% placebo), nasopharyngitis (5% CIMZIA[®], 1% placebo), back pain (4% CIMZIA[®], 1% placebo), pyrexia (3% CIMZIA[®], 2% placebo), pharyngitis (3% CIMZIA[®], 1% placebo), rash (3% CIMZIA[®], 1% placebo), acute bronchitis (3% CIMZIA[®], 1% placebo), fatigue (3% CIMZIA[®], 2% placebo). Hypertensive adverse reactions were observed more frequently in patients receiving CIMZIA[®] than in controls. These adverse reactions occurred more frequently among patients with a baseline history of hypertension and among patients receiving concomitant corticosteroids and non-steroidal anti-inflammatory drugs. Patients receiving CIMZIA[®] 400 mg as monotherapy every 4 weeks in RA controlled clinical trials had similar adverse reactions to those patients receiving CIMZIA[®] 200 mg every other week. The proportion of patients who discontinued treatment due to adverse reactions in the controlled clinical studies was 5% for CIMZIA[®] and 2.5% for placebo.

The safety profile for patients with Psoriatic Arthritis (PsA) treated with CIMZIA[®] was similar to the safety profile seen in patients with RA and previous experience with CIMZIA[®].

The safety profile for AS patients treated with CIMZIA[®] was similar to the safety profile seen in patients with RA.

For full prescribing information, please visit www.ucb.com

CIMZIA[®] is a registered trademark of the UCB Group of Companies.

References

1. CIMZIA[®] US Prescribing Information. Accessed 24th September 2015 from <http://www.ucb.com/>

For further information

- Andrea Levin Christopher, Communications Lead, Immunology, UCB, Inc.
T +1 770 970 8352, andrea.levin@ucb.com

About UCB

UCB, Brussels, Belgium (www.ucb.com) is a global biopharmaceutical company focused on the discovery and development of innovative medicines and solutions to transform the lives of people living with severe diseases of the immune system or of the central nervous system. With more than 8500 people in approximately 40 countries, the company generated revenue of € 3.3 billion in 2014. UCB is listed on Euronext Brussels (symbol: UCB). Follow us on Twitter: @UCB_news

Forward looking statements- UCB

This press release contains forward-looking statements based on current plans, estimates and beliefs of management. All statements, other than statements of historical fact, are statements that could be deemed forward-looking statements, including estimates of revenues, operating

margins, capital expenditures, cash, other financial information, expected legal, political, regulatory or clinical results and other such estimates and results. By their nature, such forward-looking statements are not guarantees of future performance and are subject to risks, uncertainties and assumptions which could cause actual results to differ materially from those that may be implied by such forward-looking statements contained in this press release.

Important factors that could result in such differences include: changes in general economic, business and competitive conditions, the inability to obtain necessary regulatory approvals or to obtain them on acceptable terms, costs associated with research and development, changes in the prospects for products in the pipeline or under development by UCB, effects of future judicial decisions or governmental investigations, product liability claims, challenges to patent protection for products or product candidates, changes in laws or regulations, exchange rate fluctuations, changes or uncertainties in tax laws or the administration of such laws and hiring and retention of its employees. UCB is providing this information as of the date of this press release and expressly disclaims any duty to update any information contained in this press release, either to confirm the actual results or to report a change in its expectations.

There is no guarantee that new product candidates in the pipeline will progress to product approval or that new indications for existing products will be developed and approved. Products or potential products which are the subject of partnerships, joint ventures or licensing collaborations may be subject to differences between the partners. Also, UCB or others could discover safety, side effects or manufacturing problems with its products after they are marketed.

Moreover, sales may be impacted by international and domestic trends toward managed care and health care cost containment and the reimbursement policies imposed by third-party payers as well as legislation affecting biopharmaceutical pricing and reimbursement.