



UCB
News

Cimzia[®] (Certolizumab Pegol) Approved by FDA for Treatment of Adults with Active Ankylosing Spondylitis

Approval represents the fourth U.S. indication for Cimzia[®]

Brussels (Belgium), 18th October 2013 – (0700 CEST) – regulated information - UCB announced today that the U.S. Food and Drug Administration (FDA) has approved Cimzia[®] (certolizumab pegol) for the treatment of adults with active ankylosing spondylitis (AS). The FDA also issued a Complete Response Letter relating to the supplemental Biologics License Application (sBLA) of Cimzia[®] for the treatment of adults with active axial spondyloarthritis (axSpA). UCB is working with the FDA to determine a path forward to bring Cimzia[®] to US patients living with active axSpA.

With these four indications, UCB confirms expected global peak sales for Cimzia[®] of at least €1.5 billion during the second half of the decade.

The approval of Cimzia[®] for adults with active AS was based on a Phase 3, multi-center, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of Cimzia[®] in patients with active axSpA, in which the majority had AS.²

“AS is a lifelong disease that can cause pain and stiffness and at times can be very debilitating for people living with it. Cimzia[®] provides an important new treatment option for people living with active AS and for rheumatologists. FDA approval of Cimzia[®] for active AS is an important milestone for UCB and bolsters Cimzia’s broad rheumatology portfolio of approved indications in the US,” said Professor Dr. Iris Loew-Friedrich, Chief Medical Officer and Executive Vice President, UCB.

In the efficacy and safety study of Cimzia[®], patients with active axSpA, including AS, were randomized (1:1:1) to receive Cimzia[®] 200 mg every two weeks, 400 mg every four weeks or placebo. There were a total of 325 patients in the study, of which 178 had AS. All patients received a loading dose with Cimzia[®] or placebo at weeks 0, 2 and 4. The primary efficacy variable, the proportion of patients achieving an ASAS20 response rate at week 12, was met with clinical and statistical significance in both dosing arms versus placebo.¹

A greater proportion of AS patients treated with Cimzia[®] 200 mg every two weeks or 400 mg every four weeks achieved ASAS20 response at week 12, compared with AS patients treated with placebo. Responses were similar in patients receiving Cimzia[®] 200 mg every two weeks and 400 mg every four weeks.¹

In this study, adverse events occurred in 70.4% of patients in the Cimzia[®] group (combined dose) compared to 62.6% of patients in the placebo group. Serious adverse events occurred in 4.7% of

patients in both the Cimzia[®] group (combined dose) and in the placebo group.² The safety profile for patients with AS treated with Cimzia[®] was similar to the safety profile seen in patients with RA and in patients with previous experience with Cimzia[®]. Please see important safety information at the end of this press release for additional details about adverse events associated with Cimzia[®].

The FDA recently approved a filing for Cimzia[®] in the treatment of adults with active psoriatic arthritis (PsA). In the U.S., Cimzia[®] is also approved for the treatment of adults with moderately to severely active rheumatoid arthritis. In addition, it is approved 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

About Cimzia[®] in Europe

In the EU, Cimzia[®] in combination with methotrexate (MTX) is approved for the treatment of moderate to severe active rheumatoid arthritis in adult patients inadequately responsive to disease-modifying anti-rheumatic drugs including MTX. Cimzia[®] can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate.³

In September 2013, the European Medicines Agency's Committee for Medicinal Products for Human Use adopted a positive opinion recommending extending the European Union marketing authorization for the use of Cimzia[®] in the treatment of adult patients with severe active axSpA. A final decision from the European Commission is expected within two months of the CHMP opinion. The European Medicines Agency is currently reviewing a filing for certolizumab pegol in the treatment of adult patients with active PsA.

About axSpA and AS

axSpA is an inflammatory rheumatic disease that mostly affects the spine and sacroiliac joints.⁴ axSpA can be further divided into ankylosing spondylitis (AS) and non-radiographic axSpA (nr-axSpA), depending on the presence or absence of definitive changes on x-ray in the sacroiliac joints (SIJ).⁵

Ankylosing Spondylitis, or AS, is a chronic inflammatory rheumatic disease of the spine⁶ and is the most well-recognized subset of axSpA.⁷ The symptoms of AS can vary, but most people experience back pain and stiffness due to inflammation which can proceed to fusion of the sacroiliac joints.⁴ The condition usually begins between 15 and 35 years of age⁶, with prevalence estimated to be .5% of the U.S. population.⁸ AS is more common in men than in women.⁶ Ankylosing spondylitis has a genetic component and is associated with the HLA-B27 gene.⁷

IMPORTANT SAFETY INFORMATION ABOUT CIMZIA[®] IN THE US

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.cimzia.com

Important Safety Information about Cimzia[®] (certolizumab pegol) IN THE EU/EEA

Cimzia[®] was studied in 4,049 patients with RA in controlled and open label trials for up to 92 months. The commonly reported adverse reactions (1-10%) in clinical trials with Cimzia[®] and post-marketing were viral infections (includes herpes, papillomavirus, influenza), bacterial infections (including abscess), rash, headache (including migraine), asthaenia, leukopaenia (including lymphopaenia, neutropaenia), eosinophilic disorder, pain (any sites), pyrexia, sensory abnormalities, hypertension, pruritus (any sites), hepatitis (including hepatic enzyme increase), injection site reactions, and

nausea. Serious adverse reactions include sepsis, opportunistic infections, tuberculosis, herpes zoster, lymphoma, leukaemia, solid organ tumours, angioneurotic oedema, cardiomyopathies (includes heart failure), ischemic coronary artery disorders, pancytopenia, hypercoagulation (including thrombophlebitis, pulmonary embolism), cerebrovascular accident, vasculitis, hepatitis/hepatopathy (includes cirrhosis), and renal impairment/nephropathy (includes nephritis). In RA controlled clinical trials, 4.4% of patients discontinued taking Cimzia® due to adverse events vs. 2.7% for placebo.

Cimzia® is contraindicated in patients with hypersensitivity to the active substance or any of the excipients, active tuberculosis or other severe infections such as sepsis or opportunistic infections or moderate to severe heart failure.

Serious infections including sepsis, tuberculosis and opportunistic infections have been reported in patients receiving Cimzia®. Some of these events have been fatal. Monitor patients closely for signs and symptoms of infections including tuberculosis before, during and after treatment with Cimzia®. Treatment with Cimzia® must not be initiated in patients with a clinically important active infection. If an infection develops, monitor carefully and stop Cimzia® if infection becomes serious. Before initiation of therapy with Cimzia®, all patients must be evaluated for both active and inactive (latent) tuberculosis infection. If active tuberculosis is diagnosed prior to or during treatment, Cimzia® therapy must not be initiated and must be discontinued. If latent tuberculosis is diagnosed, appropriate anti-tuberculosis therapy must be started before initiating treatment with Cimzia®. Patients should be instructed to seek medical advice if signs/symptoms (e.g. persistent cough, wasting/weight loss, low grade fever, listlessness) suggestive of tuberculosis occur during or after therapy with Cimzia®.

Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including Cimzia® who are chronic carriers of the virus (i.e. surface antigen positive). Some cases have had a fatal outcome. Patients should be tested for HBV infection before initiating treatment with Cimzia®. Carriers of HBV who require treatment with Cimzia® should be closely monitored and in the case of HBV reactivation Cimzia® should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

TNF antagonists including Cimzia® may increase the risk of new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease; of formation of autoantibodies and uncommonly of the development of a lupus-like syndrome; of severe hypersensitivity reactions. If a patient develops any of these adverse reactions, Cimzia® should be discontinued and appropriate therapy instituted.

With the current knowledge, a possible risk for the development of lymphomas, leukaemia or other malignancies in patients treated with a TNF antagonist cannot be excluded. Rare cases of neurological disorders, including seizure disorder, neuritis and peripheral neuropathy, have been reported in patients treated with Cimzia®.

Adverse reactions of the hematologic system, including medically significant cytopenia, have 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 haematological abnormalities.

The use of Cimzia® in combination with anakinra or abatacept is not recommended due to a potential increased risk of serious infections. As no data are available, Cimzia® should not be administered concurrently with live vaccines. The 14-day half-life of Cimzia® should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on Cimzia® should be closely monitored for infections.

Please consult the full prescribing information in relation to other side effects, full safety and prescribing information. European SmPC date of revision 12th August 2013.

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001037/WC500069763.pdf

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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 9000 people in approximately 40 countries, the company generated revenue of EUR 3.4 billion in 2012. UCB is listed on Euronext Brussels (symbol: UCB).

Forward looking statements

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.