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## U.S. FDA Arthritis Advisory Committee Votes On Cimzia<sup>®</sup> (certolizumab pegol) For Treatment of Adults with Active Axial Spondyloarthritis, Including Patients with Ankylosing Spondylitis

**BRUSSELS, 24th JULY 2013, 0700 CEST - regulated information** – UCB announced today the outcome from their participation in the U.S. Food and Drug Administration (FDA)'s Arthritis Advisory Committee to discuss its supplemental biologics application (sBLA) for Cimzia<sup>®</sup> (certolizumab pegol) for the proposed indication of treatment of adults with active axial spondyloarthritis (axSpA), including patients with ankylosing spondylitis (AS). The Arthritis Advisory Committee voted seven to six, with one Committee member abstaining, to recommend approval of Cimzia<sup>®</sup> for the proposed indication.

The FDA is not bound by the Committee's guidance, but the Agency may consider the Committee's recommendations as it completes its review of the sBLA for Cimzia<sup>®</sup> for the treatment of adults with active axSpA, including patients with ankylosing spondylitis.

"UCB is encouraged by the Committee's recommendation. Their action represents an important evidence-based, patient-focused step towards addressing the unmet needs of people living with axSpA. This condition poses significant disease burden and warrants new treatment options", said Dr. Iris Löw-Friedrich, Executive Vice-President of BioDevelopment and Chief Medical Officer, UCB. "We look forward to working with the FDA as the Agency continues its review."

The Arthritis Advisory Committee also voted on two other points regarding the data on Cimzia<sup>®</sup> for the treatment of active axSpA, including patients with ankylosing spondylitis. The Committee voted eight to five, with one Committee member abstaining, that the data provides substantial evidence that Cimzia<sup>®</sup> provides a clinically meaningful beneficial effect in the treatment of axSpA, including patients with ankylosing spondylitis. The Committee also voted 13 to one that the safety profile of Cimzia<sup>®</sup> is adequate to support approval for the treatment of active axSpA, including patients with ankylosing spondylitis.

Cimzia<sup>®</sup> is not currently approved to treat axSpA in the US or Europe. In February 2013, UCB announced two new regulatory filings with the FDA and with the European Medicines Agency (EMA) to extend the marketing authorization for Cimzia<sup>®</sup> for the treatment of adult patients with active psoriatic arthritis (PsA) and for adult patients with active axSpA. The regulatory filings for two new indications for Cimzia<sup>®</sup> are now under review by the FDA and EMA.

In the US, Cimzia® is approved for the treatment of adults with moderately to severely active rheumatoid arthritis. It is also 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.<sup>1</sup>

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.<sup>2</sup>

### **About axSpA<sup>3</sup>**

Spondyloarthritis (SpA) refers to a spectrum of inflammatory disease that affects the spine, peripheral joints, ligaments, tendons and other extraarticular tissues such as the eyes, skin and gut. SpA can be divided into peripheral and axial spondyloarthritis (axSpA), depending on the location of the predominant features. While axSpA mostly affects the spine and sacroiliac joints, peripheral SpA predominantly affects the peripheral joints. 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).

#### *Ankylosing Spondylitis<sup>3,4,6,7</sup>*

Ankylosing Spondylitis, or AS, is a chronic inflammatory rheumatic disease of the spine and is the most well-recognized subset of axSpA. 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. The condition usually begins between 15 and 35 years of age, with prevalence estimated to be .5% of the population. AS is more common in men than in women. Ankylosing spondylitis has a genetic component and is associated with the HLA-B27 gene.

#### *axSpA without radiographic evidence of AS<sup>5</sup>*

Patients are considered to have axSpA without radiographic evidence of AS (nr-axSpA) if they have no definitive sacroiliitis on conventional radiographs, but do exhibit raised inflammatory markers, similar SpA clinical features, as well as sacroiliitis on MRI or carry the HLA-B27 gene. While these patients may not have definitive structural changes in their sacroiliac joints, they share the same clinical features as AS patients and have a similar burden of disease as a result of pain, stiffness, fatigue and impairment in function.

## **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<sup>®</sup> use and during therapy. Treatment for latent infection should be initiated prior to CIMZIA<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>, 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<sup>®</sup> is a member. CIMZIA<sup>®</sup> is not indicated for use in pediatric patients.**

**Patients treated with CIMZIA<sup>®</sup> 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<sup>®</sup> should not be initiated in patients with an active infection, including clinically important localized infections. CIMZIA<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> for Crohn's disease and other investigational uses, there was one case of lymphoma among 2,657 CIMZIA<sup>®</sup>-treated patients and one case of Hodgkin lymphoma among 1,319 placebo-treated patients. In CIMZIA<sup>®</sup> 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  $\leq 18$  years of age), of which CIMZIA<sup>®</sup> 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.

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<sup>®</sup> has not been formally studied in patients with CHF. Exercise caution when using CIMZIA<sup>®</sup> 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<sup>®</sup> administration. If such reactions occur, discontinue further administration of CIMZIA<sup>®</sup> and institute appropriate therapy.

### **Hepatitis B Reactivation**

Use of TNF blockers, including CIMZIA<sup>®</sup>, 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<sup>®</sup>. Exercise caution in prescribing CIMZIA<sup>®</sup> 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<sup>®</sup> and initiate effective anti-viral therapy with appropriate supportive treatment.

### **Neurologic Reactions**

Use of TNF blockers, including CIMZIA<sup>®</sup>, 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-Barre syndrome. Rare cases of neurological disorders, including seizure disorder, optic neuritis, and peripheral neuropathy have been reported in patients treated with CIMZIA<sup>®</sup>. Exercise caution in considering the use of CIMZIA<sup>®</sup> 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<sup>®</sup>. 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<sup>®</sup>. Consider discontinuation of CIMZIA<sup>®</sup> 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<sup>®</sup> in these combinations. Therefore, the combination of CIMZIA<sup>®</sup> with anakinra, abatacept, rituximab, or natalizumab is not recommended. Interference with certain coagulation assays has been detected in patients treated with CIMZIA<sup>®</sup>. There is no evidence that CIMZIA<sup>®</sup> therapy has an effect on in vivo coagulation. CIMZIA<sup>®</sup> may cause erroneously elevated aPTT assay results in patients without coagulation abnormalities.

### **Autoimmunity**

Treatment with CIMZIA<sup>®</sup> 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<sup>®</sup>.

### **Adverse Reactions**

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

In controlled RA clinical trials, the most common adverse events that occurred in  $\geq 3\%$  of patients taking CIMZIA<sup>®</sup> 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<sup>®</sup>, 2% placebo), headache (5%

CIMZIA<sup>®</sup>, 4% placebo), hypertension (5% CIMZIA<sup>®</sup>, 2% placebo), nasopharyngitis (5% CIMZIA<sup>®</sup>, 1% placebo), back pain (4% CIMZIA<sup>®</sup>, 1% placebo), pyrexia (3% CIMZIA<sup>®</sup>, 2% placebo), pharyngitis (3% CIMZIA<sup>®</sup>, 1% placebo), rash (3% CIMZIA<sup>®</sup>, 1% placebo), acute bronchitis (3% CIMZIA<sup>®</sup>, 1% placebo), fatigue (3% CIMZIA<sup>®</sup>, 2% placebo). Hypertensive adverse reactions were observed more frequently in patients receiving CIMZIA<sup>®</sup> 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<sup>®</sup> 400mg as monotherapy every 4 weeks in RA controlled clinical trials had similar adverse reactions to those patients receiving CIMZIA<sup>®</sup> 200mg every other week. The proportion of patients who discontinued treatment due to adverse reactions in the controlled clinical studies was 5% for CIMZIA<sup>®</sup> and 2.5% for placebo.

For full prescribing information, please go to [www.ucb.com](http://www.ucb.com).

[http://www.ucb.com/up/ucb\\_com\\_products/documents/Cimzia\\_COL\\_11\\_2012.pdf](http://www.ucb.com/up/ucb_com_products/documents/Cimzia_COL_11_2012.pdf)

### **Cimzia<sup>®</sup> (certolizumab pegol) EU/EEA\* Important Safety Information**

*Cimzia<sup>®</sup> 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<sup>®</sup> and post-marketing were viral infections (includes herpes, papillomavirus, influenza), bacterial infections (including abscess), rash, headache (including migraine), asthenia, leukopenia (including lymphopenia, neutropenia), 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<sup>®</sup> due to adverse events vs. 2.7% for placebo.*

*Cimzia<sup>®</sup> 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<sup>®</sup>. 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<sup>®</sup>. Treatment with Cimzia<sup>®</sup> must not be initiated in patients with a clinically important active infection. If an infection develops, monitor carefully and stop Cimzia<sup>®</sup> if infection becomes serious. Before initiation of therapy with Cimzia<sup>®</sup>, all patients must be evaluated for both active and inactive (latent) tuberculosis infection. If active tuberculosis is diagnosed prior to or during treatment, Cimzia<sup>®</sup> 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<sup>®</sup>. 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<sup>®</sup>.*

*Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including Cimzia<sup>®</sup> 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 cytopaenia, 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 25<sup>th</sup> April 2013.*

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/001037/WC500069763.pdf](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](http://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 8 500 people in about 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.