



CIMZIA® (certolizumab pegol) label change marks important advance for European women of childbearing age with chronic rheumatic disease

- European Medicines Agency (EMA) has approved label change for UCB's CIMZIA® (certolizumab pegol), making it the first anti-TNF for potential use in women with chronic rheumatic disease, during both pregnancy and breastfeeding
- Data submitted to regulatory authorities included first-of-their-kind clinical studies demonstrating minimal transfer of CIMZIA through the placenta and breast milk from mother to infant^{1,2}
- Adequate disease control is crucial in women of childbearing age to ensure optimal infant and maternal health and to reduce adverse pregnancy outcomes

Brussels, Belgium – 9 January, 7:00 CET – UCB today announced that the European Medicines Agency (EMA) approved a label change for CIMZIA® (certolizumab pegol), making it the first anti-TNF treatment option that could be considered for women with chronic rheumatic disease, during both pregnancy and breastfeeding.

“Women of childbearing age with chronic rheumatic disease are a patient population in need of reliable treatment options and guidance. Women frequently discontinue their anti-TNF treatment throughout pregnancy, a time when disease control is essential to ensure optimal infant and maternal health. CIMZIA is the only available anti-TNF treatment that is clinically proven to show minimal placental transfer from mother to infant during pregnancy,” said Xavier Mariette, MD, PhD, Head of Rheumatology, Bicetre Hospital, Paris-Sud University.

“Today’s label change for CIMZIA is important for many European women who need treatment options to manage their chronic rheumatic disease without compromising their plans for pregnancy and breastfeeding,” said Emmanuel Caeymaex, Head of Immunology and Executive Vice President, Immunology Patient Value Unit, UCB. “UCB is executing on its Patient Value Strategy to connect the unmet needs of patients with innovative science. The research we conducted to support this label change provides critical information for physicians and women as they plan for pregnancy and appropriate disease management. This new label underscores UCB’s commitment to delivering value to underserved patient populations and improving their overall treatment experience.”

Chronic rheumatic diseases such as rheumatoid arthritis (RA), axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) frequently manifest in women of childbearing age,³ with RA, for example affecting three times more women than men.⁴ The consequences of active disease in pregnancy can have serious implications for both mother and infant, including an increased risk of miscarriage,⁵ an increased risk of preterm delivery, the need for a cesarean, and the infant being small for gestational age.⁶

Adequate disease control is crucial to ensure the best fetal and maternal health, since high disease activity during pregnancy is associated with an increased risk of adverse pregnancy outcomes.⁷⁻¹¹ Despite the perception that disease activity spontaneously improves during pregnancy, approximately 50% of women with chronic rheumatic disease need effective therapeutic intervention and are faced with difficult questions regarding the impact of active disease on their baby and the safety of different therapies during pregnancy.¹²⁻¹⁶ As such, there is an evident need for effective and well tolerated treatment during pregnancy.⁸ Additionally, women who are considering breastfeeding,

along with their treating physicians, often face a conflict between the risks of maternal medications needed for postpartum disease control and the optimal nutritional health of the child.

UCB has been leading the way in studying how biologic drugs impact women of childbearing age. Two key areas of focus are the transfer of a biologic drug through the placenta to the fetus and via the mother's breast milk to the infant. Anti-TNF lactation data historically has been based on case reports without any controlled studies. However, UCB is changing the way this research is conducted. The findings from two, first-of-their-kind studies have strong implications for this patient population as they consider pregnancy. Based on results from the landmark CRIB study, there is no to minimal placental transfer evident from mother to child during pregnancy. Data from CRADLE, the prospective pharmacokinetic trial measuring the presence of an anti-TNF in breast milk, found minimal transfer of CIMZIA during lactation.

The approval of the CIMZIA label change in the EU is based on data from the post marketing CRIB and CRADLE studies as well as our pregnancy outcomes data. The studies included women with rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, and Crohn's Disease (CD). In the EU, CIMZIA is not indicated in CD.

About the CRIB Study¹

CRIB was a pharmacokinetic study assessing the potential level of placental transfer of certolizumab pegol (CZP) from pregnant women to their infants. The study followed sixteen women (≥ 30 weeks gestation) who were already receiving CZP for approved indications.

The study found that CZP levels were below the lower limit of quantification in 13 out of 14 infant blood samples at birth, and in all samples at weeks four and eight. One infant had a minimal CZP level of 0.042 μ g/mL (infant/mother ratio of 0.09%). No anti-CZP antibodies were detected in mothers, umbilical cords, or infants. These data indicate no to minimal placental transfer of CZP from mothers to infants, suggesting lack of in utero fetal exposure during the third trimester.

In CRIB, adverse events experienced by the infants did not show any patterns or clusters of events suggesting a specific safety signal in children. Safety data in the mothers were in line with the known safety profile of CZP and pregnancy profile of these underlying diseases.

About the CRADLE Study²

The primary objectives of the CRADLE pharmacokinetic study were to determine the concentration of CZP in human breast milk and the average daily infant dose, an estimation of the daily dose of maternal CZP ingested by the infant over the dosing interval.

Among 137 breast milk samples from 17 mothers, all samples had CZP concentrations that were minimal, less than 3 times the lower limit of quantification and less than 1% of the expected therapeutic dose. A post-hoc analysis of the relative infant dose (RID) of CZP in breast milk was calculated and ranged from 0.04% to 0.30%. The RID is a useful parameter for assessing drug safety in breastfeeding and experts consider a RID that is less than 10% to be unlikely of concern to infant wellbeing.

In CRADLE, adverse events in the infants of mothers exposed to CZP were consistent with those occurring in unexposed infants of similar age. Adverse events in mothers exposed to CZP were consistent with the known safety profile of CZP.

About Pregnancy Outcomes Data

Data from more than 500 prospectively collected pregnancies exposed to CIMZIA® with known pregnancy outcomes, including more than 400 pregnancies exposed during the first trimester, does not indicate a malformative effect of CIMZIA. However, the available clinical experience is too limited to, with a reasonable certainty, conclude that there is no increased risk associated with CIMZIA administration during pregnancy. CIMZIA should only be used during pregnancy if clinically needed.

About CIMZIA® in the EU/EEA

In the EU, CIMZIA® in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active RA in adult patients inadequately responsive to disease-modifying anti-rheumatic drugs (DMARDs) including MTX.

CIMZIA can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate. CIMZIA in combination with MTX is also indicated for the treatment of severe, active and progressive RA in adults not previously treated with MTX or other DMARDs. CIMZIA has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with MTX.

CIMZIA, in combination with MTX, is also indicated for the treatment of active psoriatic arthritis in adults when the response to previous DMARD therapy has been inadequate. CIMZIA can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate.

CIMZIA is also indicated in the EU for the treatment of adult patients with severe active axial spondyloarthritis (axSpA), comprising:

- Ankylosing spondylitis (AS) – adults with severe active AS who have had an inadequate response to, or are intolerant to non-steroidal anti-inflammatory drugs (NSAIDs).
- Axial spondyloarthritis (axSpA) without radiographic evidence of AS – adults with severe active axSpA without radiographic evidence of AS but with objective signs of inflammation by elevated C-reactive protein (CRP) and/or Magnetic Resonance Imaging (MRI) who have had an inadequate response to, or are intolerant to NSAIDs.

About CIMZIA® in Fertility, Pregnancy and Lactation in the EU/EEA

Women of childbearing potential

The use of adequate contraception should be considered for women of childbearing potential. For women planning pregnancy, continued contraception may be considered for 5 months after the last CIMZIA® dose due to its elimination rate, but the need for treatment of the woman should also be taken into account (see below).

Pregnancy

Data from more than 500 prospectively collected pregnancies exposed to CIMZIA® with known pregnancy outcomes, including more than 400 pregnancies exposed during the first trimester, does not indicate a malformative effect of CIMZIA. However, the available clinical experience is too limited to, with a reasonable certainty, conclude that there is no increased risk associated with CIMZIA administration during pregnancy.

Animal studies using a rodent anti-rat TNF α did not reveal evidence of impaired fertility or harm to the foetus. However, these are insufficient with respect to human reproductive toxicity. Due to its inhibition of TNF α , CIMZIA administered during pregnancy could affect normal immune response in the newborn.

CIMZIA should only be used during pregnancy if clinically needed. Non-clinical studies suggest low or negligible level of placental transfer of a homologue Fab-fragment of certolizumab pegol (no Fc region).

In a clinical study 16 women were treated with certolizumab pegol (200 mg every 2 weeks or 400 mg every 4 weeks) during pregnancy. Certolizumab pegol plasma concentrations measured in 14 infants at birth were Below the Limit of Quantification (BLQ) in 13 samples; one was 0.042 µg/ml with an infant/mother plasma ratio at birth of 0.09%. At Week 4 and Week 8, all infant concentrations were BLQ. The clinical significance of low levels certolizumab pegol for infants is unknown. It is recommended to wait a minimum of 5 months following the mother's last CIMZIA administration during pregnancy before administration of live or live-attenuated vaccines (e.g. BCG vaccine), unless the benefit of the vaccination clearly outweighs the theoretical risk of administration of live or live-attenuated vaccines to the infants.

Breastfeeding

In a clinical study in 17 lactating women treated with CIMZIA[®], minimal transfer of certolizumab pegol from plasma to breast milk was observed. The percentage of the maternal certolizumab pegol dose that was reaching an infant during a 24 hour period was estimated to 0.04% to 0.30%. In addition, since certolizumab pegol is a protein that is degraded in the gastrointestinal tract after oral administration, the absolute bioavailability is expected to be very low in a breastfed infant. Consequently, CIMZIA can be used during breastfeeding.

Important Safety Information about CIMZIA[®] in the EU/EEA

CIMZIA[®] was studied in 4,049 patients with rheumatoid arthritis (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 haematologic 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.

CIMZIA® was studied in 325 patients with active axial spondyloarthritis (axSpA) in a placebo-controlled clinical trial for up to 30 months and in 409 patients with psoriatic arthritis (PsA) in a placebo-controlled clinical trial for up to 30 months. The safety profile for axSpA and PsA patients treated with CIMZIA® was consistent with the safety profile in RA and previous experience with CIMZIA®.

Please consult the full prescribing information in relation to other side effects, full safety and prescribing information. European SmPC date of revision December 2017.

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 more than 7,500 people in approximately 40 countries, the company generated revenue of € 4.2 billion in 2016. 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.

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REFERENCES

- ¹ Mariette X, Förger F, Abraham B, et al. Lack of Placental Transfer of Certolizumab Pegol During Pregnancy: Results from CRIB, a Prospective, Postmarketing, Multicenter, Pharmacokinetic Study. *Ann Rheum Dis*. 2017;0:1–6. doi:10.1136/annrheumdis-2017-212196.
- ² Clowse ME, Förger F, Hawng C, et al. Minimal to no transfer of certolizumab pegol into breast milk: results from CRADLE, a prospective, postmarketing, multicentre, pharmacokinetic study. *Ann Rheum Dis*. 2017;76:1890–1896.
- ³ Förger F. Treatment with biologics during pregnancy in patients with rheumatic diseases. *Rheumatologia*. 2017;55(2):57–58.
- ⁴ Gerosa M, Schioppo T, Meroni PL. Challenges and treatment options for rheumatoid arthritis during pregnancy. *Expert Opin Pharmacother*. 2016;17(11):1539–47.
- ⁵ Brouwer J, Laven JS, Hazes JM, Dolhain RJ. Miscarriages in Female Rheumatoid Arthritis Patients: Associations With Serologic Findings, Disease Activity, and Antirheumatic Drug Treatment. *Arthritis Rheumatol*. 2015;67(7):1738–43.
- ⁶ Bharti B, Lee SJ, Linday SP, et al. Disease severity and pregnancy outcomes in women with rheumatoid arthritis: results from the Organization of Teratology Information Specialists autoimmune diseases in pregnancy project. *J Rheumatol*. 2015;42:1376–1382.
- ⁷ Bröms G, Granath F, Linder M, Stephansson O, Elmberg M, Kieler H. Birth outcomes in women with inflammatory bowel disease: effects of disease activity and drug exposure. *Inflamm Bowel Dis*. 2014;20:1091–8.
- ⁸ de Man YA, Hazes JM, van der Heide H, et al. Association of higher rheumatoid arthritis disease activity during pregnancy with lower birth weight: results of a national prospective study. *Arthritis Rheum*. 2009;60:3196–206.
- ⁹ Jakobsson GL, Stephansson O, Askling J, Jacobsson LT. Pregnancy outcomes in patients with ankylosing spondylitis: a nationwide register study. *Ann Rheum Dis*. 2016;75:1838–42.
- ¹⁰ Mahadevan U, Sandborn WJ, Li DK, Hakimian S, Kane S, Corley DA. Pregnancy outcomes in women with inflammatory bowel disease: a large community-based study from Northern California. *Gastroenterology*. 2007;133:1106–12.
- ¹¹ Nørgaard M, Larsson H, Pedersen L, et al. Rheumatoid arthritis and birth outcomes: a Danish and Swedish nationwide prevalence study. *J Intern Med*. 2010;268:329–37.
- ¹² Mouyis MA, Thornton CC, Williams D, Giles IP. Pregnancy Outcomes in Patients with Psoriatic Arthritis. *J Rheumatol*. 2017;44:128–129.
- ¹³ Jethwa H, Lam S, Giles I. O26. Does Inflammatory Arthritis Really Improve During Pregnancy? A Systematic Review and Meta-Analysis. *Rheumatology*. 2014;53(1):i40–i40.
- ¹⁴ Polachek A, Li S, Polachek IS, et al. Psoriatic arthritis disease activity during pregnancy and the first-year postpartum. *Semin Arthritis Rheum*. 2017;46:740–745.
- ¹⁵ de Man YA, Dolhain RJ, van de Geijn FE, Willemsen SP, Hazes JM. Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study. *Arthritis Rheum*. 2008;59(9):1241–1248.
- ¹⁶ Pedersen N, Bortoli A, Duricova D, et al. The course of inflammatory bowel disease during pregnancy and postpartum: a prospective European ECCO-EpiCom Study of 209 pregnant women. *Aliment Pharmacol Ther*. 2013;38:501–512.