September 14, 2016

European Commission Approves Bristol-Myers Squibb's ORENCIA® (abatacept) for the Treatment of Highly Active and Progressive Disease in Adult Patients with Rheumatoid Arthritis Not Previously Treated with Methotrexate

Bristol-Myers Squibb Company announced that the European Commission approved ORENCIA® (Generic name: abatacept) intravenous (IV) infusion and subcutaneous (SC) injection, in combination with methotrexate (MTX), for the treatment of highly active and progressive disease in adult patients with rheumatoid arthritis (RA) not previously treated with MTX on September 6.

Attached is the original press release made by BMS for your information.

Orencia is a biological product that suppresses the release of cytokines by inhibiting the signals that activate T-cells and improves signs and symptoms of RA, physical functions, and health-related quality of life. Orencia was first approved for the treatment of rheumatoid arthritis in the US in December 2005. It has been approved in more than 50 countries around the world. In Japan, the manufacturing and marketing approval for Orencia IV was granted for intravenous infusion in July 2010. Orencia SC syringe formulation was approved in June 2013. Orencia SC Auto-injector was also approved in February 2016.

Ono Pharmaceutical Co., Ltd. (ONO) and Bristol-Myers Squibb (BMS) concluded a strategic partnership agreement to jointly develop and market Orencia in Japan in September 2011 and have commenced co-promotion of Orencia since June 2013.

ONO and BMS's Japan subsidiary, BMS K.K. are committed to alleviating the symptoms and improving the quality of life in RA patients who are treated with Orencia.

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European Commission Approves Bristol-Myers Squibb's ORENCIA® (abatacept) for the Treatment of Highly Active and Progressive Disease in Adult Patients with Rheumatoid Arthritis Not Previously Treated with Methotrexate

ORENCIA *is the first biologic therapy with an EU indication specifically applicable to the treatment of MTX-naive RA patients with highly active and progressive disease*

This approval marks the first time that MRI assessment of structural and inflammatory measures of disease severity are cited in SmPC to support an RA indication

(PRINCETON, N.J., September 6, 2016) - Bristol-Myers Squibb Company today announced that the European Commission has approved *ORENCIA*® (abatacept) intravenous (IV) infusion and subcutaneous (SC) injection, in combination with methotrexate (MTX), for the treatment of highly active and progressive disease in adult patients with rheumatoid arthritis (RA) not previously treated with MTX. With this approval, *ORENCIA* is the first biologic therapy with an indication in the European Union (EU) specifically applicable to the treatment of MTX-naive RA patients with highly active and progressive disease. Studies of *ORENCIA* involving adult patients with high disease activity (mean DAS28-CRP of 5.4) accompanied by poor prognostic factors for rapidly progressive disease (positive for anti-CCP antibodies (also known as ACPA), and/or RF+, presence of baseline joint erosions) provided the clinical trial evidence supporting the recommendation. This approval allows for the expanded marketing of *ORENCIA* in all 28 Member States of the EU.

"Across the globe we remain committed to advancing care for those living with RA. The European Commission's approval of *ORENCIA* in the EU for MTX-naive RA patients who have highly active and progressive disease is a testament to Bristol-Myers Squibb's commitment to advancing the science of earlier identification of patients with progressive RA prior to their suffering debilitating joint damage," said Brian J. Gavin, Vice President, *ORENCIA* Development Lead at Bristol-Myers Squibb.

The approval was based on data from two Phase 3 studies: In a 12 month, multinational, double-blind, randomized, Phase 3B study of MTX-naive patients with early, rapidly progressing RA, *ORENCIA* IV + MTX demonstrated significant efficacy vs MTX alone for those with moderate to severe RA.[1] The study, AGREE (**A**batacept study to **G**auge **R**emission and joint damage progression in MTX-naive patients with **E**arly **E**rosive RA), met its co-primary endpoints as defined by the proportion of patients achieving DAS28-CRP < 2.6 at 1 year (41% vs 23%, P<0.001) and inhibition

of radiographic progression at 1 year (mean change in total Sharp score: 0.6 vs 1.1, P=0.04).[1] Headache, upper respiratory tract infection, nasopharyngitis, and nausea were the most commonly reported adverse events occurring at a rate of ≥ 10% in patients taking *ORENCIA* in the adult RA clinical studies.[1]

The second Phase 3 data is from the AVERT (**A**ssessing **V**ery **E**arly **R**heumatoid **A**rthritis **T**reatment) study, which compared *ORENCIA* 125 mg subcutaneous + MTX combination therapy, *ORENCIA* 125 mg subcutaneous monotherapy, and MTX monotherapy in induction of DAS28-defined remission following 12 months of treatment in 351 adult patients with moderate to severe active, early RA (mean DAS28-CRP of 5.4; mean symptom duration less than 6.7 months) who had not been treated with MTX or other DMARDs earlier (MTX-naive).[2] Patients also had poor prognostic factors for rapidly progressive disease (positive for anti-CCP antibodies, and/or RF+, presence of baseline joint erosions).[2] The co-primary endpoints compared the proportion of patients with DAS28-defined remission (DAS28 CRP <2.6) at month 12 and both months 12 and 18 for *ORENCIA* + MTX versus MTX alone.[2] At 12 months, significantly more patients on *ORENCIA* combination therapy achieved DAS28-defined remission than MTX alone (60.9%, *ORENCIA* + MTX; 45.2%, MTX alone).[2] Similar results at 12 months were seen with other measures of efficacy including Boolean remission (37.0%, *ORENCIA* + MTX; 22.4%, MTX alone), CDAI remission (42%, *ORENCIA* + MTX; 27.6% MTX alone), and SDAI remission (42%, *ORENCIA* + MTX; 25% MTX alone).[2] The European Commission's approval is based on clinical response to *ORENCIA* as well as X-Ray and MRI assessments of structural and inflammatory measures of disease severity.

About Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a systemic, chronic, autoimmune disease characterized by inflammation in the lining of joints (or synovium), causing joint damage with chronic pain, stiffness, and swelling in the joints.[3,4] RA causes decreased range of motion and function in the joints.[3,4] The condition is three times more common in women than in men.[3]

U.S. Indications/Usage and Important Safety Information for ORENCIA® (abatacept)

Indication and Usage

Adult Rheumatoid Arthritis (RA): ORENCIA® (abatacept) is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and

improving physical function in adult patients with moderately to severely active RA. ORENCIA may be used as monotherapy or concomitantly with disease-modifying, anti-rheumatic drugs (DMARDs) other than tumor necrosis factor (TNF) antagonists.

Juvenile Idiopathic Arthritis (JIA): ORENCIA® (abatacept) is indicated for reducing signs and symptoms in pediatric patients aged 6 years and older with moderately to severely active polyarticular JIA. ORENCIA may be used as monotherapy or concomitantly with methotrexate (MTX).

Important Limitations of Use: ORENCIA should not be administered concomitantly with TNF antagonists, and is not recommended for use concomitantly with other biologic RA therapy, such as anakinra.

Important Safety Information for ORENCIA® (abatacept)

Concomitant Use with TNF Antagonists: Concurrent therapy with ORENCIA and a TNF antagonist is not recommended. In controlled clinical trials, adult patients receiving concomitant intravenous ORENCIA and TNF antagonist therapy experienced more infections (63%) and serious infections (4.4%) compared to patients treated with only TNF antagonists (43% and 0.8%, respectively), without an important enhancement of efficacy.

Hypersensitivity: Anaphylaxis or anaphylactoid reactions can occur during or after an infusion and can be life-threatening. There were 2 cases (<0.1%; n=2688) of anaphylaxis or anaphylactoid reactions in clinical trials with adult RA patients treated with intravenous ORENCIA. Other reactions potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, each occurred in <0.9% of patients. There was one case of a hypersensitivity reaction with ORENCIA in JIA clinical trials (0.5%; n=190). In postmarketing experience, a case of fatal anaphylaxis following the first infusion of ORENCIA was reported. Appropriate medical support measures for treating hypersensitivity reactions should be available for immediate use. If an anaphylactic or other serious allergic reaction occurs, administration of ORENCIA should be stopped immediately and permanently discontinued, with appropriate therapy instituted.

Infections: Serious infections, including sepsis and pneumonia, have been reported in patients receiving ORENCIA. Some of these infections have been fatal. Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy which, in addition to their

underlying disease, could further predispose them to infection. Caution should be exercised in patients with a history of infection or underlying conditions which may predispose them to infections. Treatment with ORENCIA should be discontinued if a patient develops a serious infection. Patients should be screened for tuberculosis and viral hepatitis in accordance with published guidelines, and if positive, treated according to standard medical practice prior to therapy with ORENCIA.

Immunizations: Live vaccines should not be given concurrently with ORENCIA or within 3 months of its discontinuation. The efficacy of vaccination in patients receiving ORENCIA is not known. ORENCIA may blunt the effectiveness of some immunizations. It is recommended that JIA patients be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating therapy with ORENCIA.

Use in Patients with Chronic Obstructive Pulmonary Disease (COPD): Adult COPD patients treated with ORENCIA developed adverse events more frequently than those treated with placebo (97% vs 88%, respectively). Respiratory disorders occurred more frequently in patients treated with ORENCIA compared to those on placebo (43% vs 24%, respectively), including COPD exacerbation, cough, rhonchi, and dyspnea. A greater percentage of patients treated with ORENCIA developed a serious adverse event compared to those on placebo (27% vs 6%), including COPD exacerbation [3 of 37 patients (8%)] and pneumonia [1 of 37 patients (3%)]. Use of ORENCIA in patients with RA and COPD should be undertaken with caution, and such patients monitored for worsening of their respiratory status.

Blood Glucose Testing: ORENCIA for intravenous administration contains maltose, which may result in falsely elevated blood glucose readings on the day of infusion when using blood glucose monitors with test strips utilizing glucose dehydrogenase pyrroloquinoline quinone (GDH-PQQ). Consider using monitors and advising patients to use monitors that do not react with maltose, such as those based on glucose dehydrogenase nicotine adenine dinucleotide (GDH-NAD), glucose oxidase or glucose hexokinase test methods. ORENCIA for subcutaneous (SC) administration does not contain maltose; therefore, patients do not need to alter their glucose monitoring.

Pregnancy: There are no adequate and well-controlled studies of ORENCIA use in pregnant women and the data with ORENCIA use in pregnant women are insufficient to inform on drug-associated risk. A pregnancy registry has been established to monitor pregnancy outcomes in women exposed to ORENCIA during pregnancy. Healthcare professionals are encouraged to register patients by calling 1-877-311-8972.

Lactation: There is no information regarding the presence of abatacept in human milk, the effects on the breastfed infant, or the effects on milk production. However, abatacept was present in the milk of lactating rats dosed with abatacept.

Most Serious Adverse Reactions: Serious infections (3% ORENCIA vs 1.9% placebo) and malignancies (1.3% ORENCIA vs 1.1% placebo).

Malignancies: The overall frequency of malignancies was similar between adult patients treated with ORENCIA or placebo. However, more cases of lung cancer were observed in patients treated with ORENCIA (0.2%) than those on placebo (0%). A higher rate of lymphoma was seen compared to the general population; however, patients with RA, particularly those with highly active disease, are at a higher risk for the development of lymphoma. The potential role of ORENCIA in the development of malignancies in humans is unknown.

Most Frequent Adverse Events (≥10%): Headache, upper respiratory tract infection, nasopharyngitis, and nausea were the most commonly reported adverse events in the adult RA clinical studies. Other events reported in ≥5% of JIA patients were diarrhea, cough, pyrexia, and abdominal pain. In general, the adverse events in pediatric patients were similar in frequency and type to those seen in adult patients.

Note concerning SC ORENCIA: The safety and efficacy of SC ORENCIA have not been studied in patients under 18 years of age.

Please see Full Prescribing Information at http://packageinserts.bms.com/pi/pi_orencia.pdf.

About Bristol-Myers Squibb Immunoscience

With a robust pipeline of immunomodulatory therapies, Bristol-Myers Squibb is committed to the discovery and development of transformational medicines that could lead to long-term remission in patients with immune-mediated diseases. As we learn more about the immune system in such diseases with substantial unmet medical needs, the potential for developing novel therapies that target specific pathways in the immune system continues to drive our research efforts.

About Bristol-Myers Squibb

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information about Bristol-Myers Squibb, visit us at BMS.com or follow us on LinkedIn, Twitter, YouTube and Facebook.

Bristol-Myers Squibb Forward-Looking Statement

This press release contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995 regarding the research, development and commercialization of pharmaceutical products. Such forward-looking statements are based on current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. No forward-looking statement can be guaranteed. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Bristol-Myers Squibb's business, particularly those identified in the cautionary factors discussion in Bristol-Myers Squibb's Annual Report on Form 10-K for the year ended December 31, 2015 in our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K. Bristol-Myers Squibb undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

References

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2. Emery P, Huizinga TW, et al. Evaluating Drug-free Remission With Abatacept in Early Rheumatoid Arthritis. Ann Rheum Dis. 2015;74(1):19-26.
3. Rheumatoid Arthritis. American College of Rheumatology. August 2012.
4. Centers for Disease Control and Prevention. Rheumatoid Arthritis. CDC Website. http://www.cdc.gov/arthritis/basics/rheumatoid.htm. Accessed May 19, 2016.

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