U.S. Food and Drug Administration Approves ORENCIA® (abatacept) for the Treatment of Moderate-to-Severe Polyarticular Juvenile Idiopathic Arthritis (JIA) in Patients Six Years and Older

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ORENCIA is a First-in-Class Biologic Treatment Option Now Available for Use in Pediatric Patients with JIA

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE: BMY) today announced that the U.S. Food and Drug Administration (FDA) has approved ORENCIA® (abatacept) for reducing signs and symptoms in pediatric patients six years and older with moderately to severely active polyarticular juvenile idiopathic arthritis (JIA). ORENCIA may be used as monotherapy or concomitantly with methotrexate (MTX). ORENCIA should not be administered concomitantly with tumor necrosis factor (TNF) antagonists and is not recommended for use concomitantly with other biologic rheumatoid arthritis (RA) therapy, such as anakinra. This new indication for ORENCIA provides significant evidence of its durable efficacy and long-term safety in pediatric patients, including those initiating biologic therapy for the first time. The safety and efficacy of ORENCIA in JIA were assessed in a three-part study through one year. The approval of ORENCIA in JIA represents the ongoing commitment of Bristol-Myers Squibb in this therapeutic area.

"In a JIA clinical trial, ORENCIA provided meaningful and sustained improvements in this patient population across three major sub-types of JIA through one year," said Edward H. Giannini, M.Sc., Dr.P.H., Professor of Pediatrics, Division of Rheumatology, Cincinnati Children's Hospital Medical Center, OH.

The approval is based on the AWAREN (A batacept W ithdrawal study to A ssess efficacy and safety in K ey E ndpoints in juvenile idiopathic arthritis N ot responding to current treatment) trial, which evaluated the efficacy and safety of ORENCIA® (abatacept) in patients six to 17 years of age with moderately to severely active polyarticular JIA who had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs), such as MTX or TNF antagonists.

"Juvenile idiopathic arthritis is the most prevalent form of arthritis in children," said Elliott Sigal, M.D., Ph.D., executive vice president, chief scientific officer and president, Research and Development, Bristol-Myers Squibb. "This new indication for ORENCIA offers another treatment option to help improve signs and symptoms of this serious disease in pediatric and adolescent patients."

In addition to the approval for JIA, Bristol-Myers Squibb has added a post-marketing safety section to the package insert. This section states that the post-marketing adverse event profile that was observed in adult RA patients did not differ from that seen in the clinical trials of adult RA patients. The FDA also has revised the adult indication to remove the requirement that patients must first fail at least one DMARD before initiating therapy with ORENCIA. The new indication statement is: ORENCIA 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 DMARDs other than TNF antagonists. ORENCIA should not be administered concomitantly with TNF antagonists and is not recommended for use concomitantly with other biologic RA therapy, such as anakinra. The revised adult indication means that ORENCIA is an appropriate option for patients with moderate-to-severe RA, regardless of prior treatment received.

ORENCIA JIA Study (AWAREN Trial)

The AWAREN trial was a three-part study which included patients with subtypes of JIA that at disease onset included Oligoarticular JIA (16 percent), Polyarticular JIA (64 percent; 20 percent were rheumatoid factor (RF) positive) and Systemic JIA with polyarticular course (20 percent) who had not responded adequately to other JIA therapies. In the first phase of this study (Period A), a total of 190 patients aged six to 17 years, with disease duration of approximately four years with moderately to severely active disease at study entry, were enrolled in this open-label, four-month, lead-in phase of the study. The majority (70 percent) of these study patients were new to biologic treatments. Nearly 30 percent of patients had previously had an inadequate response to a TNF antagonist or anakinra. Patients received ORENCIA® (abatacept)
intravenously (10 mg/kg; maximum 1,000 mg) on Days 1, 15, 29 and every month thereafter. Response was assessed utilizing the ACR Pediatric 30 definition of improvement, defined as greater than or equal to 30 percent improvement in at least three of the six JIA core set variables and greater than or equal to 30 percent worsening in not more than one of the JIA core set variables.

In Period A of the study, ORENCIA demonstrated consistent improvement in ACR Pedi 30 with similar responses across all JIA subtypes (Oligoarticular extended, 59.3 percent; Polyarticular-RF positive, 68.4 percent; Polyarticular-RF negative 64.3 percent; and Systemic JIA with polyarticular course, 64.9 percent). In patients who were inadequate responders to DMARDs including MTX and were new to biologic treatment, ORENCIA demonstrated meaningful ACR Pedi response rates with 76 percent of patients achieving an ACR Pedi 30 response rate, 60 percent achieving an ACR Pedi 50 response rate, 36 percent achieving an ACR Pedi 70 response rate and 17 percent achieving an ACR Pedi 90 response rate. In patients who received prior biological treatment, 38.6 percent achieved an ACR Pedi 30 response rate, 24.6 percent achieved an ACR Pedi 50 response rate, 10.5 percent achieved an ACR Pedi 70 response rate and 1.8 percent achieved an ACR Pedi 90 response rate.

In Period B of the study, patients who completed Period A and achieved an ACR Pedi 30 response were eligible to enter this six-month, double-blind phase. Patients entering Period B (n=122) were randomized to remain on ORENCIA (n=60) or receive placebo (n=62) for six months.

The primary endpoint of the study was time to occurrence of disease flare. Disease flare was defined as a greater than or equal to 30 percent worsening in at least three of the six JIA core set variables with greater than or equal to 30 percent improvement in not more than one of the six JIA core set variables; greater than or equal to two centimeters of worsening of the Physician or Parent Global Assessment was necessary if used as one of the three JIA core set variables used to define flare, and worsening in greater than or equal to two joints was necessary if the number of active joints or joints with limitation of motion was used as one of the three JIA core set variables used to define flare.

Efficacy results included:

- **Time difference to occurrence of disease flare** was statistically significant based on the log-rank test in patients treated with placebo compared with ORENCIA® (abatacept) (p-value equals 0.0002).
- **Patients treated with ORENCIA experienced significantly fewer disease flares** compared to placebo-treated patients (20 percent vs. 53 percent, respectively, p-value less than 0.001).
- **The risk of disease flare among patients continuing on ORENCIA was less than one-third of that for patients who withdrew from ORENCIA treatment** [Hazard Ratio: 0.31, 95 percent CI (0.16, 0.59)].

In patients receiving ORENCIA treatment throughout the study (Period A, Period B and the open-label extension Period C), the proportion of ACR Pedi 30, 50 and 70 responders remained consistent through one year.

In both the open-label, lead-in (Period A) and double-blind (Period B) phases of the study, the adverse reactions in pediatric patients were similar in type and frequency to those seen in adult patients. This was also seen in patients who participated in the open-label (Period C) extension period.

The overall frequency of adverse events in Period A was 70 percent; infections occurred at a frequency of 36 percent. The most common infections were upper respiratory tract infection and nasopharyngitis. The infections resolved without sequelae, and the types of infections were consistent with those commonly seen in outpatient pediatric populations. Other events that occurred at a prevalence of at least five percent were headache, nausea, diarrhea, cough, pyrexia and abdominal pain. A total of six serious adverse events [acute lymphocytic leukemia, ovarian cyst, varicella infection, disease flare (2) and joint wear] were reported during the initial four months of treatment with ORENCIA. There was one case of a hypersensitivity reaction (0.5 percent). During Periods A, B and C, acute infusion-related events occurred at a frequency of four percent, two percent and three percent, respectively, and were consistent with the types of events reported in adults. Upon continued treatment in the open-label extension period, the types of adverse events were similar except for a single patient diagnosed with multiple sclerosis while on open-label treatment.

**About Juvenile Idiopathic Arthritis (JIA)**

JIA -- also commonly known as Juvenile Rheumatoid Arthritis (JRA) -- is the most common chronic rheumatic disease in children, and it is an important cause of short-term and long-term disability. It is an autoimmune disease that causes chronic pain, stiffness and swelling of the joints, which may ultimately lead to joint damage and deformities. The disease usually begins before the age of 166. Juvenile arthritis may affect up to one in every 1,000 children in the United States. ORENCIA® (abatacept) is one treatment option indicated in pediatric patients ages six and older with moderately to severely active polyarticular JIA. ORENCIA may be used as monotherapy or concomitantly with MTX. ORENCIA should not be administered concomitantly with TNF antagonists and is not recommended for use concomitantly with other biological RA therapy, such as anakinra.

**Important Safety Information for ORENCIA**

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

**Hypersensitivity**: Less than one percent of adult patients treated with ORENCIA experienced hypersensitivity reactions, including some cases of anaphylaxis or anaphylactoid reactions. Other events potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, each occurred in less than 0.9 percent of patients treated with ORENCIA and generally occurred within 24 hours of infusion. There was one case of a hypersensitivity reaction with ORENCIA in JIA clinical trials (0.5 percent; n =190). Appropriate medical support measures for treating hypersensitivity reactions should be available for immediate use in the event of a reaction.
Infections: Caution should be exercised in patients with a history of infection or underlying conditions which 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® (abatacept) or within three months of its discontinuation as it 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 percent vs. 88 percent, respectively). Respiratory disorders occurred more frequently in patients treated with ORENCIA compared to those on placebo (43 percent vs. 24 percent, respectively), including COPD exacerbations, cough, rhonchi and dyspnea. A greater percentage of patients treated with ORENCIA developed a serious adverse event compared to those on placebo (27 percent vs. six percent), including COPD exacerbation (three of 37 patients [eight percent]) and pneumonia (one of 37 patients [three percent]). 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 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 pyrroloquinolinequinonine (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.

Pregnant and Nursing Mothers: ORENCIA should be used during pregnancy only if clearly needed. The risk for development of autoimmune diseases in humans exposed in utero to abatacept has not been determined. Nursing mothers should be informed of the risk/benefit of continued breast-feeding or discontinuation of the drug. A pregnancy registry has been established to monitor fetal outcomes. Healthcare professionals are encouraged to register pregnant patients exposed to ORENCIA by calling 1-877-311-8972.

Most Serious Adverse Reactions: Serious infections (three percent ORENCIA vs. 1.9 percent placebo) and malignancies (1.3 percent ORENCIA vs. 1.1 percent placebo). In general, adverse events in pediatric and adolescent patients were similar in frequency and type to those seen in adult patients.

Malignancies: The overall frequency of malignancies was similar between adult patients treated with ORENCIA® (abatacept) or placebo. However, more cases of lung cancer were observed in patients treated with ORENCIA (0.2 percent) than those on placebo (zero percent). 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 (greater than or equal to 10 percent): Headache, upper respiratory tract infection, nasopharyngitis and nausea were the most commonly reported adverse events in the adult RA clinical studies.

Please see accompanying Full Prescribing Information or visit http://www.orencia.com/ or http://www.bms.com/.

About ORENCIA
ORENCIA 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 DMARDs other than TNF antagonists. ORENCIA is also indicated for reducing signs and symptoms in pediatric patients aged six years and older with moderately to severely active polyarticular JIA. ORENCIA may be used as monotherapy or concomitantly with MTX in pediatric patients. ORENCIA should not be administered concomitantly with TNF antagonists. ORENCIA is not recommended for use concomitantly with other biologic RA therapy, such as anakinra.

For adult patients with RA, ORENCIA, a lyophilized powder for intravenous infusion, should be administered by a healthcare professional as a 30-minute intravenous infusion at a fixed dose based on body weight range approximating 10 mg/kg. Following the initial administration, ORENCIA should be given at two and four weeks after the first infusion and every four weeks thereafter. Acute infusion-related reactions were experienced in nine percent of people treated with ORENCIA and in six percent of people treated with placebo. The most frequently reported infusion-related adverse events (one percent to two percent) were dizziness, headache, and hypertension. In clinical studies, premedications were not required. However, appropriate medical support measures of the treatment of hypersensitivity reactions should be available for immediate use in the event of a reaction.

For pediatric and adolescent patients with JIA who weigh less than 75 kg, ORENCIA® (abatacept) should be administered as a 30-minute intravenous infusion at a dose of 10 mg/kg specifically calculated based on the patient’s body weight at each administration, not to exceed a maximum dose of 1000 mg. Pediatric patients weighing 75 kg or more should be administered ORENCIA following the adult dosing regimen. Following the initial administration, ORENCIA should be given at two and four weeks after the first infusion and every four weeks thereafter. ORENCIA may be used as monotherapy or concomitantly with MTX.

About Bristol-Myers Squibb
Bristol-Myers Squibb Company is a global biopharmaceutical and related health care products company whose mission is to extend and enhance human life.

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Web site: http://www.bms.com/
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5 Zeginni E. Association of HLA-DRB1*13 with susceptibility to uveitis in juvenile idiopathic arthritis in two independent data sets. Rheumatology. 2006;45:972-974.


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