

Moderate to Severe Rheumatoid Arthritis RA

Indication: ORENCIA® (abatacept) is indicated for adult patients with moderately to severely active RA to: reduce signs and symptoms, induce major clinical response, inhibit the progression of structural damage, and improve physical function. ORENCIA may be used as monotherapy or concomitantly with disease-modifying antirheumatic drugs (DMARDs) other than tumor necrosis factor (TNF) antagonists.

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.

ORENCIA is available as a lyophilized powder for intravenous (IV) infusion and as a solution for subcutaneous (SC) injection.

WITH STATS LIKE THESE
IT MAY BE TIME FOR
YOU
TO CONSIDER PUTTING
ORENCIA® (abatacept)
IN THE GAME



Please see Important Safety Information on following pages.



 Bristol-Myers Squibb

Moderate to Severe Rheumatoid Arthritis RA

Indication: ORENClA® (abatacept) is indicated for adult patients with moderately to severely active RA to: reduce signs and symptoms, induce major clinical response, inhibit the progression of structural damage, and improve physical function. ORENClA may be used as monotherapy or concomitantly with disease-modifying antirheumatic drugs (DMARDs) other than tumor necrosis factor (TNF) antagonists.

ORENCIA® (abatacept): A solid record

ORENCIA: A proven non-anti-TNF biologic

2012

More than 80,000 US adult RA patients were prescribed ORENClA since launch^{1,a,*}

2011

80% of all ORENClA patient starts in 2011 were as a first or second biologic^{2,a,†}

2011

ORENCIA is approved in subcutaneous (SC) formulation for adult patients where SC is preferred

2009

Clinical data for biologic-naïve patients with early (≤ 2 years) active moderate to severe RA added to the clinical studies section of the US Prescribing Information

2005

Approved as a first-line biologic therapy for adults with moderate to severe RA[‡]

Important Safety Information: Concomitant Use with TNF Antagonists Concurrent therapy with ORENClA and a biologic DMARD is not recommended. In controlled clinical trials, adult patients receiving concomitant intravenous ORENClA 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.

^a Based on Source Healthcare Analytics data, an anonymous database of healthcare claims. This data set, as all data sets, contains some limitations: these data cover about 40% of Rx claims and 25% of medical claims submitted and are used to project the entire population of prescribers in the US. Rx claims include claims submitted from retail and mail order pharmacies, long-term care facilities, etc; medical claims include claims submitted from physician offices, medical clinics, non-federal hospitals, etc.

[‡] Source Healthcare Analytics, PROMETIS Lx Dataset, January 2006–February 2012. NOTE: The number of patients who received at least 1 dose of ORENClA intravenous (IV) infusion or 1 dose of ORENClA subcutaneous (SC) injection. All may not currently be on treatment.

[†] Source Healthcare Analytics, PROMETIS Lx Dataset, January 2011–December 2011.

[‡] After an inadequate response to a DMARD, such as MTX. It was also indicated in patients who had an inadequate response to TNF antagonists. In 2008, the label was updated to its current indication.

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Bristol-Myers Squibb

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

ORENCIA is available as a lyophilized powder for intravenous (IV) infusion and as a solution for subcutaneous (SC) injection.

of development, trial, and usage

Helping patients do more: It starts with proven efficacy

ACQUIRE study: Compared ORENClA® (abatacept) SC + methotrexate (MTX) to ORENClA intravenous (IV) + MTX in a double-blind, double-dummy, non-inferiority, 6-month, phase IIIb, registrational trial (N=1457) in patients with an inadequate response to MTX.³

Primary endpoint: Non-inferiority of ACR 20 response rate at 6 months—76% ORENClA SC + MTX patients (n=693) vs 76% ORENClA IV + MTX patients (n=678) with estimated difference between groups of 0.3% (95% CI: -4.2, 4.8, per-protocol analysis based on prespecified margin for non-inferiority of -7.5% for the SC group).³

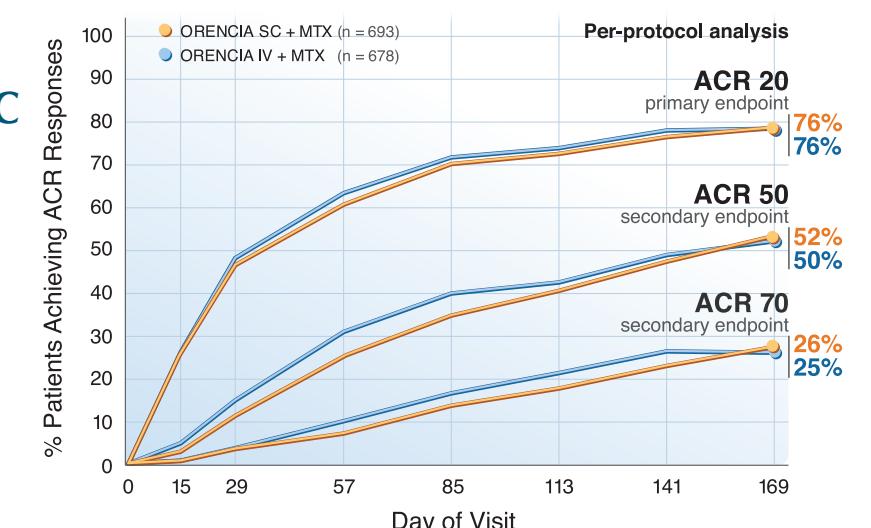
For moderate to severe RA patients for whom SC is preferred, consider ORENClA SC

Early efficacy at 3 months:

- ACR 20—Achieved by 68% and 69% of patients receiving ORENClA SC + MTX (n=693) and ORENClA IV + MTX (n=678), respectively
- ACR 50—Achieved by 33% and 39% of patients receiving ORENClA SC + MTX (n=693) and ORENClA IV + MTX (n=678), respectively

ACR 20, 50, and 70 responses continued to increase over the 6-month study period*

*The same patients may not have responded at each time point.



Study Design: Abatacept Comparison of sub(QU)cutaneous vs Intravenous in inadequate Responders to methotrexatE (ACQUIRE) was a phase IIIb, multinational, randomized, double-blind, double-dummy, non-inferiority study with 1457 adult patients with inadequate response to MTX. Patients were randomized (1:1) with stratification by body weight (<60 kg, 60-100 kg, >100 kg) to receive either—ORENCIA IV + MTX: ~10 mg/kg (based on weight range) of ORENClA IV on Days 1, 15, and 29, and every 4 weeks thereafter or ORENClA SC + MTX: ORENClA IV loading dose ~10 mg/kg (based on weight range) and 125 mg SC injection (fixed dose) on Day 1, then 125 mg SC weekly thereafter.³

Important Safety Information: Hypersensitivity Less than 1% of adult patients treated with ORENClA 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% of patients treated with ORENClA, and generally occurred within 24 hours of infusion. Appropriate medical support measures for treating hypersensitivity reactions should be available for immediate use in the event of a reaction.



See more stats at ThinkORENCIA.com and learn why ORENClA may be right for more of your appropriate RA patients.

 **ORENCIA®**
(abatacept)
Injection for Intravenous Use
Injection for Subcutaneous Use

Important Safety Information for ORENCEA® (abatacept)

Concomitant Use with TNF Antagonists:

Concurrent therapy with ORENCEA® (abatacept) and a biologic DMARD is not recommended. In controlled clinical trials, adult patients receiving concomitant intravenous ORENCEA 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: Less than 1% of adult patients treated with ORENCEA 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% of patients treated with ORENCEA, and generally occurred within 24 hours of infusion. Appropriate medical support measures for treating hypersensitivity reactions should be available for immediate use in the event of a reaction.

Infections: Serious infections, including sepsis and pneumonia, have been reported in patients receiving ORENCEA. 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 ORENCEA 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 ORENCEA.

Immunizations: Live vaccines should not be given concurrently with ORENCEA or within 3 months of its discontinuation as it may blunt the effectiveness of some immunizations.

Use in Patients with Chronic Obstructive Pulmonary Disease (COPD): Adult COPD patients treated with ORENCEA developed adverse events more frequently than those treated with placebo (97% vs 88%, respectively). Respiratory disorders occurred more frequently in patients treated with ORENCEA compared to those on placebo (43% vs 24%, respectively), including COPD exacerbations, cough, rhonchi, and dyspnea. A greater

percentage of patients treated with ORENCEA® (abatacept) 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 ORENCEA in patients with RA and COPD should be undertaken with caution, and such patients monitored for worsening of their respiratory status.

Blood Glucose Testing: ORENCEA 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 pyrroloquinolinequinone (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. ORENCEA for subcutaneous administration does not contain maltose; therefore, patients do not need to alter their glucose monitoring.

Pregnant and Nursing Mothers: ORENCEA 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 ORENCEA by calling 1-877-311-8972.

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

Malignancies: The overall frequency of malignancies was similar between adult patients treated with ORENCEA or placebo. However, more cases of lung cancer were observed in patients treated with ORENCEA (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 ORENCEA 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.

Please see brief summary of Full US Prescribing Information on adjacent page.

References: 1. Source Healthcare Analytics, PROMETIS Lx Dataset, January 2006–February 2012. 2. Source Healthcare Analytics, PROMETIS Lx Dataset, January 2011–December 2011. 3. Genovese MC, Covarrubias A, Leon G, et al. Subcutaneous abatacept versus intravenous abatacept: a phase IIIb noninferiority study in patients with an inadequate response to methotrexate. *Arthritis Rheum.* 2011;63(10):2854–2864.

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427US11AB07362 May/12



ORENCIA® (abatacept)
for injection for intravenous use
injection, for subcutaneous use

Brief Summary of Prescribing Information. For complete prescribing information, please consult official package insert.

INDICATIONS 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 rheumatoid arthritis. ORENCIA may be used as monotherapy or concomitantly with disease-modifying antirheumatic drugs (DMARDs) other than tumor necrosis factor (TNF) antagonists.

Juvenile Idiopathic Arthritis - ORENCIA is indicated for reducing signs and symptoms in pediatric patients 6 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis. ORENCIA may be used as monotherapy or concomitantly with methotrexate (MTX).

Important Limitations of Use - ORENCIA should not be administered concomitantly with TNF antagonists. ORENCIA is not recommended for use concomitantly with other biologic rheumatoid arthritis (RA) therapy, such as anakinra.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Concomitant Use with TNF Antagonists - In controlled clinical trials in patients with adult RA, 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) [see *Adverse Reactions*]. These trials failed to demonstrate an important enhancement of efficacy with concomitant administration of ORENCIA with TNF antagonist; therefore, concurrent therapy with ORENCIA and a TNF antagonist is not recommended. While transitioning from TNF antagonist therapy to ORENCIA therapy, patients should be monitored for signs of infection.

Hypersensitivity - Of 2688 patients with adult RA treated with ORENCIA intravenously in clinical trials, there were two 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% of ORENCIA-treated patients. Of the 190 patients with juvenile idiopathic arthritis treated with ORENCIA in clinical trials, there was one case of a hypersensitivity reaction (0.5%). Appropriate medical support measures for the treatment of hypersensitivity reactions should be available for immediate use in the event of a reaction [see *Adverse Reactions*].

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. Physicians should exercise caution when considering the use of ORENCIA in patients with a history of recurrent infections, underlying conditions which may predispose them to infections, or chronic, latent, or localized infections. Patients who develop a new infection while undergoing treatment with ORENCIA should be monitored closely. Administration of ORENCIA should be discontinued if a patient develops a serious infection [see *Adverse Reactions*]. A higher rate of serious infections has been observed in adult RA patients treated with concurrent TNF antagonists and ORENCIA [see *Warnings and Precautions*].

Prior to initiating immunomodulatory therapies, including ORENCIA, patients should be screened for latent tuberculosis infection with a tuberculin skin test. ORENCIA has not been studied in patients with a positive tuberculosis screen, and the safety of ORENCIA in individuals with latent tuberculosis infection is unknown. Patients testing positive in tuberculosis screening should be treated by standard medical practice prior to therapy with ORENCIA.

Antirheumatic therapies have been associated with hepatitis B reactivation. Therefore, screening for viral hepatitis should be performed in accordance with published guidelines before starting therapy with ORENCIA. In clinical studies with ORENCIA, patients who screened positive for hepatitis were excluded from study.

Immunizations - Live vaccines should not be given concurrently with ORENCIA or within 3 months of its discontinuation. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving ORENCIA. The efficacy of vaccination in patients receiving ORENCIA is not

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known. Based on its mechanism of action, ORENCIA (abatacept) may blunt the effectiveness of some immunizations.

It is recommended that patients with juvenile idiopathic arthritis be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating ORENCIA therapy.

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, including COPD exacerbations, cough, rhonchi, and dyspnea. Use of ORENCIA in patients with RA and COPD should be undertaken with caution and such patients should be monitored for worsening of their respiratory status [see *Adverse Reactions*].

Immunosuppression - The possibility exists for drugs inhibiting T cell activation, including ORENCIA, to affect host defenses against infections and malignancies since T cells mediate cellular immune responses. The impact of treatment with ORENCIA on the development and course of malignancies is not fully understood [see *Adverse Reactions*]. In clinical trials in patients with adult RA, a higher rate of infections was seen in ORENCIA-treated patients compared to placebo [see *Adverse Reactions*].

ADVERSE REACTIONS

Clinical Studies Experience in Adult RA Patients Treated with Intravenous ORENCIA - Because clinical trials are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not predict the rates observed in a broader patient population in clinical practice.

The data described herein reflect exposure to ORENCIA administered intravenously in patients with active RA in placebo-controlled studies (1955 patients with ORENCIA, 989 with placebo). The studies had either a double-blind, placebo-controlled period of 6 months (258 patients with ORENCIA, 133 with placebo) or 1 year (1697 patients with ORENCIA, 856 with placebo). A subset of these patients received concomitant biologic DMARD therapy, such as a TNF blocking agent (204 patients with ORENCIA, 134 with placebo).

The majority of patients in RA clinical studies received one or more of the following concomitant medications with ORENCIA: MTX, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, TNF blocking agents, azathioprine, chloroquine, gold, hydroxychloroquine, leflunomide, sulfasalazine, and anakinra.

The most serious adverse reactions were serious infections and malignancies.

The most commonly reported adverse events (occurring in ≥10% of patients treated with ORENCIA) were headache, upper respiratory tract infection, nasopharyngitis, and nausea.

The adverse events most frequently resulting in clinical intervention (interruption or discontinuation of ORENCIA) were due to infection. The most frequently reported infections resulting in dose interruption were upper respiratory tract infection (1.0%), bronchitis (0.7%), and herpes zoster (0.7%). The most frequent infections resulting in discontinuation were pneumonia (0.2%), localized infection (0.2%), and bronchitis (0.1%).

Infections - In the placebo-controlled trials, infections were reported in 54% of ORENCIA-treated patients and 48% of placebo-treated patients. The most commonly reported infections (reported in 5-13% of patients) were upper respiratory tract infection, nasopharyngitis, sinusitis, urinary tract infection, influenza, and bronchitis. Other infections reported in fewer than 5% of patients at a higher frequency (>0.5%) with ORENCIA compared to placebo, were rhinitis, herpes simplex, and pneumonia [see *Warnings and Precautions*].

Serious infections were reported in 3.0% of patients treated with ORENCIA and 1.9% of patients treated with placebo. The most common (0.2-0.5%) serious infections reported with ORENCIA were pneumonia, cellulitis, urinary tract infection, bronchitis, diverticulitis, and acute pyelonephritis [see *Warnings and Precautions*].

Malignancies - In the placebo-controlled portions of the clinical trials (1955 patients treated with ORENCIA for a median of 12 months), the overall frequencies of malignancies were similar in the ORENCIA- and placebo-treated patients (1.3% and 1.1%, respectively). However, more cases of lung cancer were observed in ORENCIA-treated patients (4, 0.2%) than placebo-treated patients (0). In the cumulative ORENCIA clinical trials (placebo-controlled and uncontrolled, open-label) a total of 8 cases of lung cancer (0.21 cases per 100 patient-years) and 4 lymphomas (0.10 cases per 100 patient-years) were observed in 2688 patients (3827 patient-years). The rate observed for lymphoma is approximately 3.5-fold higher than expected in an age- and gender-matched general population based on the National Cancer Institute's Surveillance, Epidemiology, and End

Results Database. Patients with RA, particularly those with highly active disease, are at a higher risk for the development of lymphoma. Other malignancies included skin, breast, bile duct, bladder, cervical, endometrial, lymphoma, melanoma, myelodysplastic syndrome, ovarian, prostate, renal, thyroid, and uterine cancers [see *Warnings and Precautions*]. The potential role of ORENCIA (abatacept) in the development of malignancies in humans is unknown.

Infusion-Related Reactions and Hypersensitivity Reactions

Acute infusion-related events (adverse reactions occurring within 1 hour of the start of the infusion) in Studies III, IV, and V [see *Clinical Studies (14.1)* in Full Prescribing Information] were more common in the ORENCIA-treated patients than the placebo patients (9% for ORENCIA, 6% for placebo). The most frequently reported events (1-2%) were dizziness, headache, and hypertension.

Acute infusion-related events that were reported in >0.1% and ≤1% of patients treated with ORENCIA included cardiopulmonary symptoms, such as hypotension, increased blood pressure, and dyspnea; other symptoms included nausea, flushing, urticaria, cough, hypersensitivity, pruritus, rash, and wheezing. Most of these reactions were mild (68%) to moderate (28%). Fewer than 1% of ORENCIA-treated patients discontinued due to an acute infusion-related event. In controlled trials, 6 ORENCIA-treated patients compared to 2 placebo-treated patients discontinued study treatment due to acute infusion-related events.

Of 2688 patients treated with ORENCIA in clinical trials, there were two 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% of ORENCIA-treated patients and generally occurred within 24 hours of ORENCIA infusion. Appropriate medical support measures for the treatment of hypersensitivity reactions should be available for immediate use in the event of a reaction [see *Warnings and Precautions*].

Adverse Reactions in Patients with COPD - In Study V [see *Clinical Studies (14.1)* in Full Prescribing Information], there were 37 patients with chronic obstructive pulmonary disease (COPD) who were treated with ORENCIA and 17 COPD patients who were treated with placebo. The 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 ORENCIA-treated patients compared to placebo-treated patients (43% vs 24%, respectively) including COPD exacerbation, cough, rhonchi, and dyspnea. A greater percentage of ORENCIA-treated patients developed a serious adverse event compared to placebo-treated patients (27% vs 6%), including COPD exacerbation (3 of 37 patients [8%]) and pneumonia (1 of 37 patients [3%]) [see *Warnings and Precautions*].

Other Adverse Reactions - Adverse events occurring in 3% or more of patients and at least 1% more frequently in ORENCIA-treated patients (n=1955) versus placebo (n=989) during placebo-controlled RA studies were: Headache (18%, 13%); Nasopharyngitis (12%, 9%); Dizziness (9%, 7%); Cough (8%, 7%); Back pain (7%, 6%); Hypertension (7%, 4%); Dyspepsia (6%, 4%); Urinary tract infection (6%, 5%); Rash (4%, 3%); Pain in extremity (3%, 2%), respectively. The ORENCIA group included 204 patients on concomitant biologic DMARDs (adalimumab, anakinra, etanercept, or infliximab). The placebo group included 134 patients on concomitant biologic DMARDs (adalimumab, anakinra, etanercept, or infliximab).

Immunogenicity - Antibodies directed against the entire abatacept molecule or to the CTLA-4 portion of abatacept were assessed by ELISA assays in RA patients for up to 2 years following repeated treatment with ORENCIA. Thirty-four of 1993 (1.7%) patients developed binding antibodies to the entire abatacept molecule or to the CTLA-4 portion of abatacept. Because trough levels of abatacept can interfere with assay results, a subset analysis was performed. In this analysis it was observed that 9 of 154 (5.8%) patients that had discontinued treatment with ORENCIA for over 56 days developed antibodies. Samples with confirmed binding activity to CTLA-4 were assessed for the presence of neutralizing antibodies in a cell-based luciferase reporter assay. Six of 9 (67%) evaluable patients were shown to possess neutralizing antibodies. However, the development of neutralizing antibodies may be underreported due to lack of assay sensitivity.

No correlation of antibody development to clinical response or adverse events was observed.

The data reflect the percentage of patients whose test results were positive for antibodies to abatacept in specific assays. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons,

comparison of the incidence of antibodies to abatacept with the incidence of antibodies to other products may be misleading.

Clinical Experience in MTX-Naïve Patients - Study VI was an active-controlled clinical trial in MTX-naïve patients [see *Clinical Studies (14.1)* in Full Prescribing Information]. The safety experience in these patients was consistent with Studies I-V.

Clinical Experience in Adult RA Patients Treated with Subcutaneous ORENCIA (abatacept) - Because clinical trials are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not predict the rates observed in a broader patient population in clinical practice.

Study SC-I was a randomized, double-blind, double-dummy, non-inferiority study that compared the efficacy and safety of abatacept administered subcutaneously (SC) and intravenously (IV) in 1457 subjects with rheumatoid arthritis, receiving background MTX, and experiencing an inadequate response to MTX (MTX-IR) [see *Clinical Studies (14.1)* in Full Prescribing Information]. The safety experience and immunogenicity for ORENCIA administered subcutaneously was consistent with intravenous Studies I-VI. Due to the route of administration, injection site reactions and immunogenicity were evaluated in Study SC-I and two other smaller studies discussed in the sections below.

Injection Site Reactions in Adult RA Patients Treated with Subcutaneous ORENCIA - Study SC-I compared the safety of abatacept including injection site reactions following subcutaneous or intravenous administration. The overall frequency of injection site reactions was 2.6% (19/736) and 2.5% (18/721) for the subcutaneous abatacept group and the intravenous abatacept group (subcutaneous placebo), respectively. All these injection site reactions (including hematoma, pruritus, and erythema) were mild (83%) to moderate (17%) in severity, and none necessitated drug discontinuation.

Immunogenicity in Adult RA Patients Treated with Subcutaneous ORENCIA - Study SC-I compared the immunogenicity to abatacept following subcutaneous or intravenous administration. The overall immunogenicity frequency to abatacept was 1.1% (8/725) and 2.3% (16/710) for the subcutaneous and intravenous groups, respectively. The rate is consistent with previous experience, and there was no correlation of immunogenicity with effects on pharmacokinetics, safety, or efficacy.

Immunogenicity and Safety of Subcutaneous ORENCIA Administration as Monotherapy without an Intravenous Loading Dose - Study SC-II was conducted to determine the effect of monotherapy use of ORENCIA on immunogenicity following subcutaneous administration without an intravenous load in 100 RA patients, who had not previously received abatacept or other CTLA4 Ig, who received either subcutaneous ORENCIA plus MTX (n=51) or subcutaneous ORENCIA monotherapy (n=49). No patients in either group developed anti-product antibodies after 4 months of treatment. The safety observed in this study was consistent with that observed in the other subcutaneous studies.

Immunogenicity and Safety of Subcutaneous ORENCIA upon Withdrawal (Three Months) and Restart of Treatment - Study SC-III in the subcutaneous program was conducted to investigate the effect of withdrawal (three months) and restart of ORENCIA subcutaneous treatment on immunogenicity in RA patients treated concomitantly with MTX. One hundred sixty-seven patients were enrolled in the first 3-month treatment period and responders (n=120) were randomized to either subcutaneous ORENCIA or placebo for the second 3-month period (withdrawal period). Patients from this period then received open-label ORENCIA treatment in the final 3-month period of the study (period 3). At the end of the withdrawal period, 0/38 patients who continued to receive subcutaneous ORENCIA developed anti-product antibodies compared to 7/73 (9.6%) of patients who had subcutaneous ORENCIA withdrawn during this period. Half of the patients receiving subcutaneous placebo during the withdrawal period received a single intravenous infusion of ORENCIA at the start of period 3 and half received intravenous placebo. At the end of period 3, when all patients again received subcutaneous ORENCIA, the immunogenicity rates were 1/38 (2.6%) in the group receiving subcutaneous ORENCIA throughout, and 2/73 (2.7%) in the group that had received placebo during the withdrawal period. Upon reinitiating therapy, there were no injection reactions and no differences in response to therapy in patients who were withdrawn from subcutaneous therapy for up to 3 months relative to those who remained on subcutaneous therapy, whether therapy was reintroduced with or without an intravenous loading dose. The safety observed in this study was consistent with that observed in the other studies.

Clinical Studies Experience in Juvenile Idiopathic Arthritis -

In general, the adverse events in pediatric patients were similar in frequency and type to those seen in adult patients [see *Warnings and Precautions, Adverse Reactions*].

ORENCIA (abatacept) has been studied in 190 pediatric patients, 6 to 17 years of age, with polyarticular juvenile idiopathic arthritis. Overall frequency of adverse events in the 4-month, lead-in, open-label period of the study was 70%; infections occurred at a frequency of 36% [see *Clinical Studies (14.2)* in Full Prescribing Information]. 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 5% were headache, nausea, diarrhea, cough, pyrexia, and abdominal pain.

A total of 6 serious adverse events (acute lymphocytic leukemia, ovarian cyst, varicella infection, disease flare [2], and joint wear) were reported during the initial 4 months of treatment with ORENCIA.

Of the 190 patients with juvenile idiopathic arthritis treated with ORENCIA in clinical trials, there was one case of a hypersensitivity reaction (0.5%). During Periods A, B, and C, acute infusion-related reactions occurred at a frequency of 4%, 2%, and 3%, 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 in frequency and type to those seen in adult patients, except for a single patient diagnosed with multiple sclerosis while on open-label treatment.

Immunogenicity - Antibodies directed against the entire abatacept molecule or to the CTLA-4 portion of abatacept were assessed by ELISA assays in patients with juvenile idiopathic arthritis following repeated treatment with ORENCIA throughout the open-label period. For patients who were withdrawn from therapy for up to 6 months during the double-blind period, the rate of antibody formation to the CTLA-4 portion of the molecule was 41% (22/54), while for those who remained on therapy the rate was 13% (7/54). Twenty of these patients had samples that could be tested for antibodies with neutralizing activity; of these, 8 (40%) patients were shown to possess neutralizing antibodies. The presence of antibodies was generally transient and titers were low. The presence of antibodies was not associated with adverse events, changes in efficacy, or an effect on serum concentrations of abatacept. For patients who were withdrawn from ORENCIA during the double-blind period for up to 6 months, no serious acute infusion-related events were observed upon re-initiation of ORENCIA therapy.

Postmarketing Experience - Adverse reactions have been reported during the postapproval use of ORENCIA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to ORENCIA. Based on the postmarketing experience in adult RA patients, the following adverse reaction has been identified during postapproval use with ORENCIA.

- Vasculitis (including cutaneous vasculitis and leukocytoclastic vasculitis)

DRUG INTERACTIONS

TNF Antagonists - Concurrent administration of a TNF antagonist with ORENCIA has been associated with an increased risk of serious infections and no significant additional efficacy over use of the TNF antagonists alone. Concurrent therapy with ORENCIA and TNF antagonists is not recommended [see *Warnings and Precautions*].

Other Biologic RA Therapy - There is insufficient experience to assess the safety and efficacy of ORENCIA administered concurrently with other biologic RA therapy, such as anakinra, and therefore such use is not recommended.

Blood Glucose Testing - Parenteral drug products containing maltose can interfere with the readings of blood glucose monitors that use test strips with glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ). The GDH-PQQ based glucose monitoring systems may react with the maltose present in ORENCIA for intravenous administration, resulting in falsely elevated blood glucose readings on the day of infusion. When receiving ORENCIA through intravenous administration, patients that require blood glucose monitoring should be advised to consider methods 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 administration does not contain maltose; therefore, patients do not need to alter their glucose monitoring.

USE IN SPECIFIC POPULATIONS

Pregnancy - Pregnancy Category C: There are no adequate and well-controlled studies of ORENCIA (abatacept) use in pregnant women. Abatacept has been shown to cross the placenta in animals, and in animal reproduction studies alterations in immune function occurred. ORENCIA should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Abatacept was not teratogenic when administered to pregnant mice at doses up to 300 mg/kg and in pregnant rats and rabbits at doses up to 200 mg/kg daily representing approximately 29 times the exposure associated with the maximum recommended human dose (MRHD) of 10 mg/kg based on AUC (area under the time-concentration curve).

Abatacept administered to female rats every three days during early gestation and throughout the lactation period, produced no adverse effects in offspring at doses up to 45 mg/kg, representing 3 times the exposure associated with the MRHD of 10 mg/kg based on AUC. However, at 200 mg/kg, 11 times the MRHD exposure, alterations in immune function were observed consisting of a 9-fold increase in T-cell dependent antibody response in female pups and thyroid inflammation in one female pup. It is not known whether these findings indicate a risk for development of autoimmune diseases in humans exposed *in utero* to abatacept. However, exposure to abatacept in the juvenile rat, which may be more representative of the fetal immune system state in the human, resulted in immune system abnormalities including inflammation of the thyroid and pancreas [see *Nonclinical Toxicology (13.2)* in Full Prescribing Information].

Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to ORENCIA, a pregnancy registry has been established. Healthcare professionals are encouraged to register patients and pregnant women are encouraged to enroll themselves by calling 1-877-311-8972.

Nursing Mothers - It is not known whether ORENCIA is excreted into human milk or absorbed systemically after ingestion by a nursing infant. However, abatacept was excreted in rat milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ORENCIA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use - ORENCIA is indicated for reducing signs and symptoms in pediatric patients with moderately to severely active polyarticular juvenile idiopathic arthritis ages 6 years and older. ORENCIA may be used as monotherapy or concomitantly with MTX.

Studies in juvenile rats exposed to ORENCIA prior to immune system maturity have shown immune system abnormalities including an increase in the incidence of infections leading to death as well as inflammation of the thyroid and pancreas [see *Nonclinical Toxicology (13.2)* in Full Prescribing Information]. Studies in adult mice and monkeys have not demonstrated similar findings. As the immune system of the rat is undeveloped in the first few weeks after birth, the relevance of these results to humans greater than 6 years of age (where the immune system is largely developed) is unknown.

ORENCIA is not recommended for use in patients below the age of 6 years.

The safety and effectiveness of ORENCIA in pediatric patients below 6 years of age have not been established. The safety and efficacy of ORENCIA in pediatric patients for uses other than juvenile idiopathic arthritis have not been established.

Geriatric Use - A total of 323 patients 65 years of age and older, including 53 patients 75 years and older, received ORENCIA in clinical studies. No overall differences in safety or effectiveness were observed between these patients and younger patients, but these numbers are too low to rule out differences. The frequency of serious infection and malignancy among ORENCIA-treated patients over age 65 was higher than for those under age 65. Because there is a higher incidence of infections and malignancies in the elderly population in general, caution should be used when treating the elderly.

OVERDOSAGE

Doses up to 50 mg/kg have been administered intravenously without apparent toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

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