

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ORENCIA safely and effectively. See full prescribing information for ORENCIA.

### ORENCIA (abatacept)

#### Lyophilized Powder for Intravenous Infusion

Initial U.S. Approval: 2005

#### -----INDICATIONS AND USAGE-----

ORENCIA is a selective T cell costimulation modulator indicated for:

##### Adult Rheumatoid Arthritis (RA) (1.1)

- moderately to severely active RA in adults. ORENCIA may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists (1.1).

##### Juvenile Idiopathic Arthritis (1.2)

- moderately to severely active polyarticular juvenile idiopathic arthritis in pediatric patients 6 years of age and older. ORENCIA may be used as monotherapy or concomitantly with MTX (1.2).

##### Important Limitations of Use (1.3)

- should not be given concomitantly with TNF antagonists (1.3, 5.1).

#### -----DOSAGE AND ADMINISTRATION-----

##### Adult RA (2.1)

Body Weight of Patient	Dose	Number of Vials
<60 kg	500 mg	2
60 to 100 kg	750 mg	3
>100 kg	1000 mg	4

##### Juvenile Idiopathic Arthritis (2.2)

- Pediatric patients weighing less than 75 kg receive 10 mg/kg based on the patient's body weight. Pediatric patients weighing 75 kg or more should be administered ORENCIA following the adult dosing regimen, not to exceed a maximum dose of 1000 mg (2.2).

##### General Dosing Information (2)

- Administer as a 30-minute intravenous infusion (2)
- Following initial dose, give at 2 and 4 weeks, then every 4 weeks (2)
- Prepare ORENCIA using only the silicone-free disposable syringe (2.3)

#### -----DOSAGE FORMS AND STRENGTHS-----

- 250 mg single-use vial (3)

#### -----CONTRAINDICATIONS-----

- None (4)

#### -----WARNINGS AND PRECAUTIONS-----

- Concomitant use with a TNF antagonist can increase the risk of infections and serious infections (5.1)
- Hypersensitivity, anaphylaxis, and anaphylactoid reactions (5.2)
- Patients with a history of recurrent infections or underlying conditions predisposing to infections may experience more infections (5.3, 8.5)
- Discontinue if a serious infection develops (5.3)
- Screen for latent TB infection prior to initiating therapy. Patients testing positive should be treated prior to initiating ORENCIA (5.3)
- Live vaccines should not be given concurrently or within 3 months of discontinuation (5.4)
- Patients with juvenile idiopathic arthritis should be brought up to date with all immunizations prior to ORENCIA therapy (5.4)
- Based on its mechanism of action, ORENCIA may blunt the effectiveness of some immunizations (5.4)
- COPD patients may develop more frequent respiratory adverse events (5.5)

#### -----ADVERSE REACTIONS-----

Most common adverse events (≥10%) are headache, upper respiratory tract infection, nasopharyngitis, and nausea (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

#### -----USE IN SPECIFIC POPULATIONS-----

- Pregnancy: Registry available. Based on animal data, may cause fetal harm (8.1).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 08/2009

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## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

#### **1.1 Adult Rheumatoid Arthritis (RA)**

ORENCIA<sup>®</sup> 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.

#### **1.2 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).

#### **1.3 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.

### **2 DOSAGE AND ADMINISTRATION**

#### **2.1 Adult Rheumatoid Arthritis**

For adult patients with RA, ORENCIA should be administered as a 30-minute intravenous infusion utilizing the weight range-based dosing specified in Table 1. Following the initial administration, ORENCIA should be given at 2 and 4 weeks after the first infusion and every 4 weeks thereafter. ORENCIA may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.

For pediatric juvenile idiopathic arthritis, a dose calculated based on each patient's body weight is used [see *Dosage and Administration* (2.2)].

**Table 1: Dose of ORENCIA in Adult RA**

Body Weight of Patient	Dose	Number of Vials <sup>a</sup>
<60 kg	500 mg	2
60 to 100 kg	750 mg	3
>100 kg	1000 mg	4

<sup>a</sup> Each vial provides 250 mg of abatacept for administration.

## 2.2 Juvenile Idiopathic Arthritis

The recommended dose of ORENCIA for patients 6 to 17 years of age with juvenile idiopathic arthritis who weigh less than 75 kg is 10 mg/kg calculated based on the patient's body weight at each administration. Pediatric patients weighing 75 kg or more should be administered ORENCIA following the adult dosing regimen, not to exceed a maximum dose of 1000 mg. ORENCIA should be administered as a 30-minute intravenous infusion. Following the initial administration, ORENCIA should be given at 2 and 4 weeks after the first infusion and every 4 weeks thereafter. Any unused portions in the vials must be immediately discarded.

## 2.3 Preparation and Administration Instructions

**Use aseptic technique.**

ORENCIA is provided as a lyophilized powder in preservative-free, single-use vials. Each ORENCIA vial provides 250 mg of abatacept for administration. The ORENCIA powder in each vial must be reconstituted with 10 mL of Sterile Water for Injection, USP, using **ONLY the SILICONE-FREE DISPOSABLE SYRINGE PROVIDED WITH EACH VIAL** and an 18- to 21-gauge needle. After reconstitution, the concentration of abatacept in the vial will be 25 mg/mL. If the ORENCIA powder is accidentally reconstituted using a siliconized syringe, the solution may develop a few translucent particles. Discard any solutions prepared using siliconized syringes.

If the **SILICONE-FREE DISPOSABLE SYRINGE** is dropped or becomes contaminated, use a new **SILICONE-FREE DISPOSABLE SYRINGE** from inventory. For information on obtaining additional **SILICONE-FREE DISPOSABLE SYRINGES**, contact Bristol-Myers Squibb 1-800-ORENCIA.

During reconstitution, to minimize foam formation in solutions of ORENCIA, the vial should be rotated with gentle swirling until the contents are completely dissolved. Avoid prolonged or vigorous agitation. **DO NOT SHAKE**. Upon complete dissolution of the lyophilized powder, the

vial should be vented with a needle to dissipate any foam that may be present. The solution should be clear and colorless to pale yellow. Do not use if opaque particles, discoloration, or other foreign particles are present.

- 1) To reconstitute the ORENCIA powder, remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of Sterile Water for Injection, USP, to the glass wall of the vial. Do not use the vial if the vacuum is not present. Rotate the vial with gentle swirling until the contents are completely dissolved.
- 2) Upon complete dissolution of the lyophilized powder, the vial should be vented with a needle to dissipate any foam that may be present. After reconstitution, each milliliter will contain 25 mg (250 mg/10 mL).
- 3) The reconstituted ORENCIA solution must be further diluted to 100 mL as follows. From a 100 mL infusion bag or bottle, withdraw a volume of 0.9% Sodium Chloride Injection, USP, equal to the volume of the reconstituted ORENCIA solution required for the patient's dose. Slowly add the reconstituted ORENCIA solution into the infusion bag or bottle using the same SILICONE-FREE DISPOSABLE SYRINGE PROVIDED WITH EACH VIAL. Gently mix. DO NOT SHAKE THE BAG OR BOTTLE. The final concentration of abatacept in the bag or bottle will depend upon the amount of drug added, but will be no more than 10 mg/mL. Any unused portions in the vials must be immediately discarded.
- 4) Prior to administration, the ORENCIA solution should be inspected visually for particulate matter and discoloration. Discard the solution if any particulate matter or discoloration is observed.
- 5) The entire, fully diluted ORENCIA solution should be administered over a period of 30 minutes and must be administered with an infusion set and a **STERILE, NON-PYROGENIC, LOW-PROTEIN-BINDING FILTER** (pore size of 0.2 µm to 1.2 µm).
- 6) The infusion of the fully diluted ORENCIA solution must be completed within 24 hours of reconstitution of the ORENCIA vials. The fully diluted ORENCIA solution may be stored at room temperature or refrigerated at 2°C to 8°C (36°F to 46°F) before use.
- 7) ORENCIA should not be infused concomitantly in the same intravenous line with other agents. No physical or biochemical compatibility studies have been conducted to evaluate the coadministration of ORENCIA with other agents.

### **3            DOSAGE FORMS AND STRENGTHS**

250 mg single-use vial

### **4            CONTRAINDICATIONS**

None.

### **5            WARNINGS AND PRECAUTIONS**

#### **5.1           Concomitant Use with TNF Antagonists**

In controlled clinical trials in patients with adult RA, patients receiving concomitant 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 (6.1)*]. 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.

#### **5.2           Hypersensitivity**

Of 2688 patients with adult RA 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. 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 (6.1, 6.2)*].

#### **5.3           Infections**

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 (6.1)*]. A higher rate of serious infections has been observed in adult RA patients treated with concurrent TNF antagonists and ORENCIA [see *Warnings and Precautions (5.1)*].

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.

## **5.4 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 known. Based on its mechanism of action, ORENCIA 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.

## **5.5 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* (6.1)].

## **5.6 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* (6.1)]. 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* (6.1)].

## **6 ADVERSE REACTIONS**

### **6.1 Clinical Studies Experience in Adult RA**

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 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  $\geq 10\%$  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* (5.3)].

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* (5.3)].

## **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 Surveillance, Epidemiology, and End Results Database.<sup>1</sup> 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* (5.6)]. The potential role of ORENCIA 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)] 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 to moderate. 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* (5.2)].

## Adverse Reactions in Patients with COPD

In Study V [see *Clinical Studies* (14.1)], 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* (5.5)].

## Other Adverse Reactions

Adverse events occurring in 3% or more of patients and at least 1% more frequently in ORENCIA-treated patients during placebo-controlled RA studies are summarized in Table 2.

**Table 2: Adverse Events Occurring in 3% or More of Patients and at Least 1% More Frequently in ORENCIA-Treated Patients During Placebo-Controlled RA Studies**

Adverse Event (Preferred Term)	ORENCIA (n=1955) <sup>a</sup> Percentage	Placebo (n=989) <sup>b</sup> Percentage
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

<sup>a</sup> Includes 204 patients on concomitant biologic DMARDs (adalimumab, anakinra, etanercept, or infliximab).

<sup>b</sup> Includes 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.

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-Naive Patients

Study VI was an active-controlled clinical trial in MTX-naive patients [see *Clinical Studies (14.1)*]. The safety experience in these patients was consistent with Studies I-V.

## 6.2 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 (5)*, *Adverse Reactions (6)*].

ORENCIA 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)*]. 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).

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.

## **6.3 Postmarketing Experience**

Adverse reactions have been reported during the post-approval 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 with ORENCIA in adult RA patients, the adverse event profile of ORENCIA does not differ from that listed/discussed above in Section 6.1 in adults.

## **7 DRUG INTERACTIONS**

### **7.1 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* (5.1)].

### **7.2 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.

### **7.3 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, resulting in falsely elevated blood glucose readings on the day of infusion. When receiving ORENCIA, 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.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### **Pregnancy Category C**

There are no adequate and well-controlled studies of ORENCIA 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)].

*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.

### **8.3 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.

### **8.4 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)]. 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.

The safety and effectiveness of ORENCIA in pediatric patients below 6 years of age have not been established. Therefore, ORENCIA is not recommended for use in patients below the age of 6 years.

Safety and efficacy of ORENCIA in pediatric patients for uses other than juvenile idiopathic arthritis have not been established.

## **8.5 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.

## **10 OVERDOSAGE**

ORENCIA is administered as an intravenous infusion under medically controlled conditions. Doses up to 50 mg/kg have been administered without apparent toxic effect. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

## **11 DESCRIPTION**

ORENCIA (abatacept) is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to the modified Fc (hinge, CH2, and CH3 domains) portion of human immunoglobulin G1 (IgG1). Abatacept is produced by recombinant DNA technology in a mammalian cell expression system. The apparent molecular weight of abatacept is 92 kilodaltons.

ORENCIA is supplied as a sterile, white, preservative-free, lyophilized powder for parenteral administration. Following reconstitution with 10 mL of Sterile Water for Injection, USP, the solution of ORENCIA is clear, colorless to pale yellow, with a pH range of 7.2 to 7.8. Each single-use vial of ORENCIA provides 250 mg abatacept, 500 mg maltose, 17.2 mg monobasic sodium phosphate, and 14.6 mg sodium chloride for administration.

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

Abatacept, a selective costimulation modulator, inhibits T cell (T lymphocyte) activation by binding to CD80 and CD86, thereby blocking interaction with CD28. This interaction provides a costimulatory signal necessary for full activation of T lymphocytes. Activated T lymphocytes are implicated in the pathogenesis of RA and are found in the synovium of patients with RA.

*In vitro*, abatacept decreases T cell proliferation and inhibits the production of the cytokines TNF alpha (TNF $\alpha$ ), interferon- $\gamma$ , and interleukin-2. In a rat collagen-induced arthritis model, abatacept suppresses inflammation, decreases anti-collagen antibody production, and reduces antigen specific production of interferon- $\gamma$ . The relationship of these biological response markers to the mechanisms by which ORENCIA exerts its effects in RA is unknown.

### **12.2 Pharmacodynamics**

In clinical trials with ORENCIA at doses approximating 10 mg/kg, decreases were observed in serum levels of soluble interleukin-2 receptor (sIL-2R), interleukin-6 (IL-6), rheumatoid factor (RF), C-reactive protein (CRP), matrix metalloproteinase-3 (MMP3), and TNF $\alpha$ . The relationship of these biological response markers to the mechanisms by which ORENCIA exerts its effects in RA is unknown.

### **12.3 Pharmacokinetics**

#### **Healthy Adults and Adult RA**

The pharmacokinetics of abatacept were studied in healthy adult subjects after a single 10 mg/kg intravenous infusion and in RA patients after multiple 10 mg/kg intravenous infusions (see Table 3).

**Table 3: Pharmacokinetic Parameters (Mean, Range) in Healthy Subjects and RA Patients After 10 mg/kg Intravenous Infusion(s)**

<b>PK Parameter</b>	<b>Healthy Subjects (After 10 mg/kg Single Dose) n=13</b>	<b>RA Patients (After 10 mg/kg Multiple Doses<sup>a</sup>) n=14</b>
Peak Concentration (C <sub>max</sub> ) [mcg/mL]	292 (175-427)	295 (171-398)
Terminal half-life (t <sub>1/2</sub> ) [days]	16.7 (12-23)	13.1 (8-25)
Systemic clearance (CL) [mL/h/kg]	0.23 (0.16-0.30)	0.22 (0.13-0.47)
Volume of distribution (V <sub>ss</sub> ) [L/kg]	0.09 (0.06-0.13)	0.07 (0.02-0.13)

<sup>a</sup> Multiple intravenous infusions were administered at days 1, 15, 30, and monthly thereafter.

The pharmacokinetics of abatacept in RA patients and healthy subjects appeared to be comparable. In RA patients, after multiple intravenous infusions, the pharmacokinetics of abatacept showed proportional increases of C<sub>max</sub> and AUC over the dose range of 2 mg/kg to 10 mg/kg. At 10 mg/kg, serum concentration appeared to reach a steady-state by day 60 with a mean (range) trough concentration of 24 (1 to 66) mcg/mL. No systemic accumulation of abatacept occurred upon continued repeated treatment with 10 mg/kg at monthly intervals in RA patients.

Population pharmacokinetic analyses in RA patients revealed that there was a trend toward higher clearance of abatacept with increasing body weight. Age and gender (when corrected for body weight) did not affect clearance. Concomitant MTX, NSAIDs, corticosteroids, and TNF blocking agents did not influence abatacept clearance.

No formal studies were conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of abatacept.

### **Juvenile Idiopathic Arthritis**

In patients 6 to 17 years of age, the mean (range) steady-state serum peak and trough concentrations of abatacept were 217 (57 to 700) and 11.9 (0.15 to 44.6) mcg/mL. Population pharmacokinetic analyses of the serum concentration data showed that clearance of abatacept increased with baseline body weight. The estimated mean (range) clearance of abatacept in the juvenile idiopathic arthritis patients was 0.4 (0.20 to 1.12) mL/h/kg. After accounting for the effect of body weight, the clearance of abatacept was not related to age and gender. Concomitant methotrexate, corticosteroids, and NSAIDs were also shown not to influence abatacept clearance.



## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

In a mouse carcinogenicity study, weekly subcutaneous injections of 20, 65, or 200 mg/kg of abatacept administered for up to 84 weeks in males and 88 weeks in females were associated with increases in the incidence of malignant lymphomas (all doses) and mammary gland tumors (intermediate- and high-dose in females). The mice from this study were infected with murine leukemia virus and mouse mammary tumor virus. These viruses are associated with an increased incidence of lymphomas and mammary gland tumors, respectively, in immunosuppressed mice. The doses used in these studies produced exposures 0.8, 2.0, and 3.0 times higher, respectively, than the exposure associated with the maximum recommended human dose (MRHD) of 10 mg/kg based on AUC (area under the time-concentration curve). The relevance of these findings to the clinical use of ORENCIA is unknown.

In a one-year toxicity study in cynomolgus monkeys, abatacept was administered intravenously once weekly at doses up to 50 mg/kg (producing 9 times the MRHD exposure based on AUC). Abatacept was not associated with any significant drug-related toxicity. Reversible pharmacological effects consisted of minimal transient decreases in serum IgG and minimal to severe lymphoid depletion of germinal centers in the spleen and/or lymph nodes. No evidence of lymphomas or preneoplastic morphologic changes was observed, despite the presence of a virus (lymphocryptovirus) known to cause these lesions in immunosuppressed monkeys within the time frame of this study. The relevance of these findings to the clinical use of ORENCIA is unknown.

No mutagenic potential of abatacept was observed in the *in vitro* bacterial reverse mutation (Ames) or Chinese hamster ovary/hypoxanthine guanine phosphoribosyl-transferase (CHO/HGPRT) forward point mutation assays with or without metabolic activation, and no chromosomal aberrations were observed in human lymphocytes treated with abatacept with or without metabolic activation.

Abatacept had no adverse effects on male or female fertility in rats at doses up to 200 mg/kg every three days (11 times the MRHD exposure based on AUC).

### **13.2 Animal Toxicology and/or Pharmacology**

A juvenile animal study was conducted in rats dosed with abatacept from 4 to 94 days of age in which an increase in the incidence of infections leading to death occurred at all doses compared with controls. Altered T-cell subsets including increased T-helper cells and reduced T-regulatory cells were observed. In addition, inhibition of T-cell-dependent antibody responses (TDAR) was

observed. Upon following these animals into adulthood, lymphocytic inflammation of the thyroid and pancreatic islets was observed.

In studies of adult mice and monkeys, inhibition of TDAR was apparent. However, infection and mortality, altered T-helper cells, and inflammation of thyroid and pancreas were not observed.

## **14 CLINICAL STUDIES**

### **14.1 Adult Rheumatoid Arthritis**

The efficacy and safety of ORENCIA were assessed in six randomized, double-blind, controlled studies (five placebo-controlled and one active-controlled) in patients  $\geq 18$  years of age with active RA diagnosed according to American College of Rheumatology (ACR) criteria. Studies I, II, III, IV, and VI required patients to have at least 12 tender and 10 swollen joints at randomization. Study V did not require any specific number of tender or swollen joints. ORENCIA or placebo treatment was given intravenously at weeks 0, 2, and 4 and then every 4 weeks thereafter.

Study I evaluated ORENCIA as monotherapy in 122 patients with active RA who had failed at least one non-biologic DMARD or etanercept. In Study II and Study III, the efficacy and safety of ORENCIA were assessed in patients with an inadequate response to MTX and who were continued on their stable dose of MTX. In Study IV, the efficacy and safety of ORENCIA were assessed in patients with an inadequate response to a TNF blocking agent, with the TNF blocking agent discontinued prior to randomization; other DMARDs were permitted. Study V primarily assessed safety in patients with active RA requiring additional intervention in spite of current therapy with DMARDs; all DMARDs used at enrollment were continued. Patients in Study V were not excluded for comorbid medical conditions. In Study VI, the efficacy and safety of ORENCIA were assessed in MTX-naïve patients with RA of less than 2 years disease duration. In Study VI, patients previously naïve to MTX were randomized to receive ORENCIA plus MTX or MTX plus placebo.

Study I patients were randomized to receive one of three doses of ORENCIA (0.5, 2, or 10 mg/kg) or placebo ending at week 8. Study II patients were randomized to receive ORENCIA 2 or 10 mg/kg or placebo for 12 months. Study III, IV, V, and VI patients were randomized to receive a dose of ORENCIA based on weight range or placebo for 12 months (Studies III, V, and VI) or 6 months (Study IV). The dose of ORENCIA was 500 mg for patients weighing less than 60 kg, 750 mg for patients weighing 60 to 100 kg, and 1000 mg for patients weighing greater than 100 kg.

## Clinical Response

The percent of ORENCIA-treated patients achieving ACR 20, 50, and 70 responses and major clinical response in Studies I, III, IV, and VI are shown in Table 4. ORENCIA-treated patients had higher ACR 20, 50, and 70 response rates at 6 months compared to placebo-treated patients. Month 6 ACR response rates in Study II for the 10 mg/kg group were similar to the ORENCIA group in Study III.

In Studies III and IV, improvement in the ACR 20 response rate versus placebo was observed within 15 days in some patients and within 29 days versus MTX in Study VI. In Studies II, III, and VI, ACR response rates were maintained to 12 months in ORENCIA-treated patients. ACR responses were maintained up to three years in the open-label extension of Study II.

In Study VI, a greater proportion of patients treated with ORENCIA plus MTX achieved a low level of disease activity as measured by a DAS28-CRP less than 2.6 at 12 months compared to those treated with MTX plus placebo (Table 4). Of patients treated with ORENCIA plus MTX who achieved DAS28-CRP less than 2.6, 54% had no active joints, 17% had one active joint, 7% had two active joints, and 22% had three or more active joints, where an active joint was a joint that was rated as tender or swollen or both.

**Table 4: Clinical Responses in Controlled Trials**

	Percent of Patients							
	Inadequate Response to DMARDs		Inadequate Response to MTX		Inadequate Response to TNF Blocking Agent		MTX-Naive	
	Study I		Study III		Study IV		Study VI	
Response Rate	ORN <sup>a</sup> n=32	PBO n=32	ORN <sup>b</sup> +MTX n=424	PBO +MTX n=214	ORN <sup>b</sup> +DMARDs n=256	PBO +DMARDs n=133	ORN <sup>b</sup> +MTX n=256	PBO +MTX n=253
<b>ACR 20</b>								
Month 3	53%	31%	62%***	37%	46%***	18%	64%*	53%
Month 6	NA	NA	68%***	40%	50%***	20%	75%**	62%
Month 12	NA	NA	73%***	40%	NA	NA	76%***	62%
<b>ACR 50</b>								
Month 3	16%	6%	32%***	8%	18%**	6%	40%***	23%
Month 6	NA	NA	40%***	17%	20%***	4%	53%***	38%
Month 12	NA	NA	48%***	18%	NA	NA	57%***	42%
<b>ACR 70</b>								
Month 3	6%	0	13%***	3%	6%*	1%	19%**	10%
Month 6	NA	NA	20%***	7%	10%**	2%	32%**	20%
Month 12	NA	NA	29%***	6%	NA	NA	43%***	27%
<b>Major Clinical Response<sup>c</sup></b>	NA	NA	14%***	2%	NA	NA	27%***	12%
<b>DAS28-CRP &lt;2.6<sup>d</sup></b>								
Month 12	NA	NA	NA	NA	NA	NA	41%***	23%

\* p<0.05, ORENCIA (ORN) vs placebo (PBO) or MTX.

\*\* p<0.01, ORENCIA vs placebo or MTX.

\*\*\* p<0.001, ORENCIA vs placebo or MTX.

<sup>a</sup> 10 mg/kg.

<sup>b</sup> Dosing based on weight range [see *Dosage and Administration (2.1)*].

<sup>c</sup> Major clinical response is defined as achieving an ACR 70 response for a continuous 6-month period.

<sup>d</sup> Refer to text for additional description of remaining joint activity.

The results of the components of the ACR response criteria for Studies III and IV are shown in Table 5. In ORENCIA-treated patients, greater improvement was seen in all ACR response criteria components through 6 and 12 months than in placebo-treated patients.

**Table 5: Components of ACR Response at 6 Months**

Component (median)	Inadequate Response to MTX				Inadequate Response to TNF Blocking Agent			
	Study III				Study IV			
	ORENCIA +MTX n=424		Placebo +MTX n=214		ORENCIA +DMARDs n=256		Placebo +DMARDs n=133	
	Baseline	Month 6	Baseline	Month 6	Baseline	Month 6	Baseline	Month 6
Number of tender joints (0-68)	28	7***	31	14	30	13***	31	24
Number of swollen joints (0-66)	19	5***	20	11	21	10***	20	14
Pain <sup>a</sup>	67	27***	70	50	73	43**	74	64
Patient global assessment <sup>a</sup>	66	29***	64	48	71	44***	73	63
Disability index <sup>b</sup>	1.75	1.13***	1.75	1.38	1.88	1.38***	2.00	1.75
Physician global assessment <sup>a</sup>	69	21***	68	40	71	32***	69	54
CRP (mg/dL)	2.2	0.9***	2.1	1.8	3.4	1.3***	2.8	2.3

\*\* p<0.01, ORENCIA vs placebo, based on mean percent change from baseline.

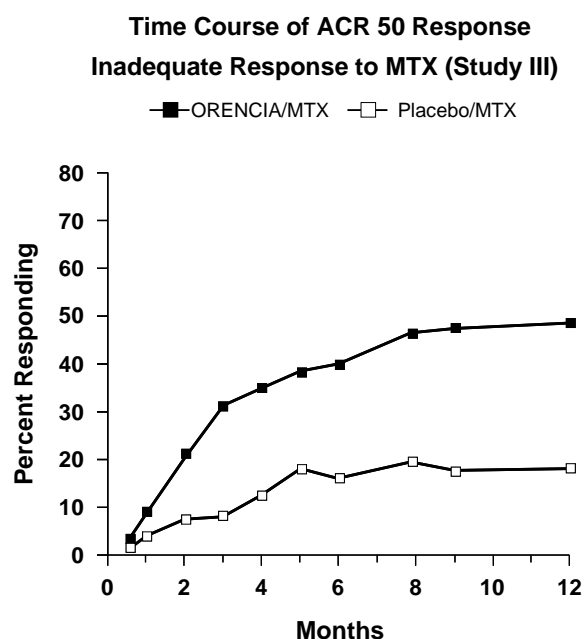
\*\*\* p<0.001, ORENCIA vs placebo, based on mean percent change from baseline.

<sup>a</sup> Visual analog scale: 0 = best, 100 = worst.

<sup>b</sup> Health Assessment Questionnaire: 0 = best, 3 = worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

The percent of patients achieving the ACR 50 response for Study III by visit is shown in Figure 1. The time course for the ORENCIA group in Study VI was similar to that in Study III.

**Figure 1: Percent of Patients Achieving ACR 50 Response by Visit\* (Study III)**



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

ORENCIA-treated patients experienced greater improvement than placebo-treated patients in morning stiffness.

### **Radiographic Response**

In Study III and Study VI, structural joint damage was assessed radiographically and expressed as change from baseline in the Genant-modified Total Sharp Score (TSS) and its components, the Erosion Score (ES) and Joint Space Narrowing (JSN) score. ORENCIA/MTX slowed the progression of structural damage compared to placebo/MTX after 12 months of treatment as shown in Table 6.

**Table 6: Mean Radiographic Changes in Study III<sup>a</sup> and Study VI<sup>b</sup>**

Parameter	ORENCIA/MTX	Placebo/MTX	Differences	P-value <sup>d</sup>
Study III				
First Year				
TSS	1.07	2.43	1.36	<0.01
ES	0.61	1.47	0.86	<0.01
JSN score	0.46	0.97	0.51	<0.01
Second Year				
TSS	0.48	0.74 <sup>c</sup>	-	-
ES	0.23	0.22 <sup>c</sup>	-	-
JSN score	0.25	0.51 <sup>c</sup>	-	-
Study VI				
First Year				
TSS	0.6	1.1	0.5	0.04

<sup>a</sup> patients with an inadequate response to MTX.

<sup>b</sup> MTX-naïve patients.

<sup>c</sup> Patients received 1 year of placebo/MTX followed by 1 year of ORENCIA/MTX.

<sup>d</sup> Based on a nonparametric ANCOVA model.

In the open-label extension of Study III, 75% of patients initially randomized to ORENCIA/MTX and 65% of patients initially randomized to placebo/MTX were evaluated radiographically at Year 2. As shown in Table 6, progression of structural damage in ORENCIA/MTX-treated patients was further reduced in the second year of treatment.

Following 2 years of treatment with ORENCIA/MTX, 51% of patients had no progression of structural damage as defined by a change in the TSS of zero or less compared with baseline. Fifty-six percent (56%) of ORENCIA/MTX-treated patients had no progression during the first year compared to 45% of placebo/MTX-treated patients. In their second year of treatment with ORENCIA/MTX, more patients had no progression than in the first year (65% vs 56%).

### Physical Function Response and Health-Related Outcomes

Improvement in physical function was measured by the Health Assessment Questionnaire Disability Index (HAQ-DI). In the HAQ-DI, ORENCIA demonstrated greater improvement from baseline versus placebo in Studies II-V and versus MTX in Study VI. The results from Studies II and III are shown in Table 7. Similar results were observed in Study V compared to placebo and in Study VI compared to MTX. During the open-label period of Study II, the improvement in physical function has been maintained for up to 3 years.

**Table 7: Mean Improvement from Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI)**

	Inadequate Response to Methotrexate			
	Study II		Study III	
	ORENCIA <sup>a</sup> +MTX (n=115)	Placebo +MTX (n=119)	ORENCIA <sup>b</sup> +MTX (n=422)	Placebo +MTX (n=212)
HAQ Disability Index				
Baseline (Mean)	0.98 <sup>c</sup>	0.97 <sup>c</sup>	1.69 <sup>d</sup>	1.69 <sup>d</sup>
Mean Improvement Year 1	0.40 <sup>c***</sup>	0.15 <sup>c</sup>	0.66 <sup>d***</sup>	0.37 <sup>d</sup>

\*\*\* p<0.001, ORENCIA vs placebo.

<sup>a</sup> 10 mg/kg.

<sup>b</sup> Dosing based on weight range [see *Dosage and Administration (2.1)*].

<sup>c</sup> Modified Health Assessment Questionnaire: 0 = best, 3 = worst; 8 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

<sup>d</sup> Health Assessment Questionnaire: 0 = best, 3 = worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

Health-related quality of life was assessed by the SF-36 questionnaire at 6 months in Studies II, III, and IV and at 12 months in Studies II and III. In these studies, improvement was observed in the ORENCIA group as compared with the placebo group in all 8 domains of the SF-36 as well as the Physical Component Summary (PCS) and the Mental Component Summary (MCS).

## 14.2 Juvenile Idiopathic Arthritis

The safety and efficacy of ORENCIA were assessed in a three-part study including an open-label extension in children with polyarticular juvenile idiopathic arthritis (JIA). Patients 6 to 17 years of age (n=190) with moderately to severely active polyarticular JIA who had an inadequate response to one or more DMARDs, such as MTX or TNF antagonists, were treated. Patients had a disease duration of approximately 4 years with moderately to severely active disease at study entry, as determined by baseline counts of active joints (mean, 16) and joints with loss of motion (mean, 16); patients had elevated C-reactive protein (CRP) levels (mean, 3.2 mg/dL) and ESR (mean, 32 mm/h). The patients enrolled had subtypes of JIA that at disease onset included Oligoarticular (16%), Polyarticular (64%; 20% were rheumatoid factor positive), and Systemic (20%). At study entry, 74% of patients were receiving MTX (mean dose, 13.2 mg/m<sup>2</sup> per week) and remained on a stable dose of MTX (those not receiving MTX did not initiate MTX treatment during the study).

In Period A (open-label, lead-in), patients received 10 mg/kg (maximum 1000 mg per dose) intravenously on days 1, 15, 29, and monthly thereafter. Response was assessed utilizing the



ACR Pediatric 30 definition of improvement, defined as  $\geq 30\%$  improvement in at least 3 of the 6 JIA core set variables and  $\geq 30\%$  worsening in not more than 1 of the 6 JIA core set variables. Patients demonstrating an ACR Pedi 30 response at the end of Period A were randomized into the double-blind phase (Period B) and received either ORENCIA or placebo for 6 months or until disease flare. Disease flare was defined as a  $\geq 30\%$  worsening in at least 3 of the 6 JIA core set variables with  $\geq 30\%$  improvement in not more than 1 of the 6 JIA core set variables;  $\geq 2$  cm of worsening of the Physician or Parent Global Assessment was necessary if used as 1 of the 3 JIA core set variables used to define flare, and worsening in  $\geq 2$  joints was necessary if the number of active joints or joints with limitation of motion was used as 1 of the 3 JIA core set variables used to define flare.

At the conclusion of Period A, pediatric ACR 30/50/70 responses were 65%, 50%, and 28%, respectively. Pediatric ACR 30 responses were similar in all subtypes of JIA studied.

During the double-blind randomized withdrawal phase (Period B), ORENCIA-treated patients experienced significantly fewer disease flares compared to placebo-treated patients (20% vs 53%); 95% CI of the difference (15%, 52%). The risk of disease flare among patients continuing on ORENCIA was less than one third than that for patients withdrawn from ORENCIA treatment (hazard ratio=0.31, 95% CI [0.16, 0.59]). Among patients who received ORENCIA throughout the study (Period A, Period B, and the open-label extension Period C), the proportion of pediatric ACR 30/50/70 responders has remained consistent for 1 year.

## **15 REFERENCES**

1. Ries LAG, Eisner MP, Kosary CL, et al. SEER Cancer Statistics Review, 1975-2001, National Cancer Institute. Bethesda, MD, [http://seer.cancer.gov/csr/1975\\_2001/](http://seer.cancer.gov/csr/1975_2001/). Accessed 2004.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

ORENCIA<sup>®</sup> (abatacept) lyophilized powder for intravenous infusion is supplied as an individually packaged, single-use vial with a silicone-free disposable syringe. The product is available in the following strength: NDC 0003-2187-10, providing 250 mg of abatacept in a 15-mL vial.

### **Storage**

Store in a refrigerator, 2°C to 8°C (36°F to 46°F). Do not use beyond the expiration date. Protect the vials from light by storing in the original package until time of use.

## **17 PATIENT COUNSELING INFORMATION**

See FDA-Approved Patient Labeling (17.7)

### **17.1 Concomitant Use With Biologic Medications for RA**

Patients should be informed that they should not receive ORENCIA treatment concomitantly with a TNF antagonist, such as adalimumab, etanercept, and infliximab because such combination therapy may increase their risk for infections [see *Indications and Usage* (1.3), *Warnings and Precautions* (5.1), and *Drug Interactions* (7.1)], and that they should not receive ORENCIA concomitantly with other biologic RA therapy, such as anakinra because there is not enough information to assess the safety and efficacy of such combination therapy [see *Indications and Usage* (1.3), and *Drug Interactions* (7.2)].

### **17.2 Hypersensitivity**

Patients should be instructed to immediately tell their healthcare professional if they experience symptoms of an allergic reaction during or for the first day after the administration of ORENCIA [see *Warnings and Precautions* (5.2)].

### **17.3 Infections**

Patients should be asked if they have a history of recurrent infections, have underlying conditions which may predispose them to infections, or have chronic, latent, or localized infections. Patients should be asked if they have had tuberculosis (TB), a positive skin test for TB, or recently have been in close contact with someone who has had TB. Patients should be instructed that they may be tested for TB before they receive ORENCIA. Patients should be informed to tell their healthcare professional if they develop an infection during therapy with ORENCIA [see *Warnings and Precautions* (5.3)].

### **17.4 Immunizations**

Patients should be informed that live vaccines should not be given concurrently with ORENCIA or within 3 months of its discontinuation. Caregivers of patients with juvenile idiopathic arthritis should be informed that the patient should be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating ORENCIA therapy and to discuss with their healthcare provider how best to handle future immunizations once ORENCIA therapy has been initiated [see *Warnings and Precautions* (5.4)].

## **17.5 Pregnancy and Nursing Mothers**

Patients should be informed that ORENCIA has not been studied in pregnant women or nursing mothers so the effects of ORENCIA on pregnant women or nursing infants are not known. Patients should be instructed to tell their healthcare professional if they are pregnant, become pregnant, or are thinking about becoming pregnant [see *Use in Specific Populations* (8.1)]. Patients should be instructed to tell their healthcare professional if they plan to breast-feed their infant [see *Use in Specific Populations* (8.3)].

## **17.6 Blood Glucose Testing**

Patients should be asked if they have diabetes. Maltose contained in ORENCIA can give falsely elevated blood glucose readings with certain blood glucose monitors on the day of ORENCIA infusion. If a patient is using such a monitor, the patient should be advised to discuss with their healthcare professional methods that do not react with maltose [see *Drug Interactions* (7.3)].

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Bristol-Myers Squibb Company  
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Rev August 2009

## 17.7 FDA-Approved Patient Labeling

### PATIENT INFORMATION

## **ORENCIA<sup>®</sup>** (oh-REN-see-ah) **(abatacept)**

Read this Patient Information before you start receiving ORENCIA and each time before you are scheduled to receive ORENCIA. The information may have changed. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

### **What is ORENCIA?**

ORENCIA is a prescription medicine that reduces signs and symptoms in:

- adults with moderate to severe rheumatoid arthritis (RA), including those who have not been helped enough by other medicines for RA. ORENCIA may prevent further damage to your bones and joints and may help your ability to perform daily activities.
- children and adolescents 6 years of age and older with moderate to severe polyarticular juvenile idiopathic arthritis (JIA).

In RA and JIA, ORENCIA can reduce pain and joint inflammation, but it can also make your immune system less able to fight infection. ORENCIA can make you more likely to get infections or make any infection you have worse. It is important to tell your doctor if you think you have any infections.

ORENCIA has not been studied in children under 6 years of age.

### **What should I tell my doctor before treatment with ORENCIA?**

Before you receive ORENCIA you should tell your doctor about all your medical conditions, including if you:

- have any kind of infection even if it is small (such as an open cut or sore), or an infection that is in your whole body (such as the flu). If you have an infection when taking ORENCIA, you may have a higher chance for getting serious side effects.
- have an infection that will not go away or a history of infections that keep coming back.
- have had tuberculosis (TB), a positive skin test for TB, or you recently have been in close contact with someone who has had TB. If you get any of the symptoms of TB (a dry cough that doesn't go away, weight loss, fever, night sweats) call your doctor right away. Before you start ORENCIA, your doctor may examine you for TB or perform a skin test.

- have or have had viral hepatitis. Before you use ORENCIA, your doctor may examine you for hepatitis.
- have a history of chronic obstructive pulmonary (lung) disease (COPD).
- are scheduled to have surgery.
- are allergic to any of the ingredients in ORENCIA. See the end of this leaflet for a list of the ingredients in ORENCIA.
- recently received a vaccination or are scheduled for any vaccination. If you are receiving ORENCIA, you should not take live vaccines.
- have diabetes and use a blood glucose monitor to check your blood sugar (blood glucose) levels. ORENCIA contains maltose, a type of sugar that can give false high blood sugar readings with certain types of blood glucose monitors, on the day of ORENCIA infusion. Your doctor may tell you to use a different way to monitor your blood sugar levels.
- are pregnant or planning to become pregnant. It is not known if ORENCIA can harm your unborn baby.

Bristol-Myers Squibb Company has a registry for pregnant women exposed to ORENCIA. The purpose of this registry is to check the health of the pregnant mother and her child. Patients are encouraged to call the registry themselves or ask their doctors to contact the registry for them by calling 1-877-311-8972.

- are breast-feeding. ORENCIA can pass into breast milk. Women who are breast-feeding should talk to their doctor about whether or not to use ORENCIA.

**Tell your doctor about all the medicines you take**, including prescription and non-prescription medicines, vitamins, and herbal supplements. Do not start taking any new medicine without talking with your doctor.

Especially tell your doctor if you take other biologic medicines to treat RA or JIA that may affect your immune system, such as:

- Enbrel<sup>®</sup> (etanercept)
- Humira<sup>®</sup> (adalimumab)
- Remicade<sup>®</sup> (infliximab)
- Kineret<sup>®</sup> (anakinra)
- Rituxan<sup>®</sup> (rituximab)

You may have a higher chance of getting a serious infection if you take ORENCIA with other biologic medicines for your RA or JIA.

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new prescription.

## How will I receive ORENCIA?

- You will be given ORENCIA by a healthcare provider through a needle placed in a vein (IV or intravenous infusion) in your arm. It takes about 30 minutes to give you the full dose of medicine.
- You will receive ORENCIA 2 weeks and 4 weeks after the first dose. You will then receive ORENCIA every 4 weeks.
- If you miss your appointment to receive ORENCIA, ask your doctor when to schedule your next dose.

## What are the possible side effects of ORENCIA?

ORENCIA can cause serious side effects including:

- **Serious infections.** Patients receiving ORENCIA have a higher chance of getting infections including pneumonia, and other infections caused by viruses, bacteria, or fungi. Call your doctor right away if you feel sick or get any of the following symptoms of infection, which may be early signs of a serious infection:
  - a fever
  - feel very tired
  - have a cough
  - have flu-like symptoms
  - warm, red, or painful skin
- **Allergic reactions.** Allergic reactions can happen on the day of treatment or the day after receiving ORENCIA. Tell your doctor or get emergency medical help right away if you have hives, swollen face, eyelids, lips, tongue, throat, or trouble breathing.
- **Cancer (malignancies).** Certain kinds of cancer have been reported in patients receiving ORENCIA. It is not known if ORENCIA increases your chance of getting certain kinds of cancer.
- **Vaccinations.** You should not receive ORENCIA with certain types of vaccines (live vaccines). ORENCIA may also cause some vaccinations to be less effective. Talk with your doctor about your vaccination plans.
- **Respiratory problems in patients with Chronic Obstructive Pulmonary Disease (COPD).** You may get certain respiratory problems more often if you receive ORENCIA and have COPD, including:
  - worsened COPD
  - pneumonia
  - cough
  - trouble breathing

## **Common side effects of ORENCIA in both adults and children include:**

- headache
- upper respiratory tract infection
- sore throat
- nausea

## **In children, other side effects may include:**

- diarrhea
- cough
- fever
- abdominal pain

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of ORENCIA. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

## **General information about ORENCIA**

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use ORENCIA for a condition for which it was not prescribed.

This patient information leaflet summarizes the most important information that you need to know about ORENCIA. If you would like more information, talk to your doctor.

You can ask your pharmacist or doctor for information about ORENCIA that is written for health professionals. For more information, go to [www.ORENCIA.com](http://www.ORENCIA.com) or the company internet site at [www.BMS.com](http://www.BMS.com) or call 1-800-ORENCIA toll-free.

## **What are the ingredients in ORENCIA?**

Active ingredient: abatacept

Inactive ingredients: maltose, monobasic sodium phosphate, sodium chloride for administration

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