FULL PRESCRIBING INFORMATION

NAME OF THE MEDICINAL PRODUCT

ORENCIA 125 MG SC AND ORENCIA 250 MG

QUALITATIVE AND QUANTITATIVE COMPOSITION

For Orencia 250 mg IV: 250 mg white to off-white lyophilized powder in a single-dose vial (one may use less than the full contents of the vial or use more than one vial) *[see Dosage and Administration (2.1, 2.2, 2.3)]*.

For Orencia 125 mg SC: 125 mg/mL of a clear to slightly opalescent, colorless to pale-yellow solution in a single-dose prefilled glass syringe

PHARMACEUTICAL FORM

Orencia 250 mg IV- Powder (lyophilized) for concentrate for solution for IV infusion.

Orencia 125 mg SC- Solution for Subcutaneous Injection

1. THERAPEUTIC INDICATIONS

1.1 ORENCIA 125 mg:

Adult Rheumatoid Arthritis (RA)

ORENCIA is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis.

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

Adult Psoriatic Arthritis

ORENCIA is indicated for the treatment of adult patients with active psoriatic arthritis (PsA).

1.2 ORENCIA 250 mg:

Adult Rheumatoid Arthritis (RA)

ORENCIA is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis.

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

Polyarticular juvenile idiopathic arthritis:

ORENCIA in combination with methotrexate is indicated for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis (JIA) in pediatric patients 6 years of age and older who have had an insufficient response to other DMARDs including at least one TNF inhibitor. ORENCIA has not been studied in children under 6 years old.

Adult Psoriatic Arthritis (PsA)

ORENCIA is indicated for the treatment of adult patients with active psoriatic arthritis (PsA).

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 may be administered as an intravenous infusion or as a subcutaneous injection.

ORENCIA may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.

Intravenous Dosing Regimen

ORENCIA lyophilized powder should be reconstituted and administered after dilution [*see Dosage and Administration (2.3)*] as a 30-minute intravenous infusion utilizing the weight range-based dosing specified in Table 1. Following the initial intravenous administration, an intravenous infusion should be given at 2 and 4 weeks after the first infusion and every 4 weeks thereafter.

Table 1: Dose of ORENCIA for Intravenous Infusion in Adult RA Patients

Body Weight of Patient	Dose	Number of Vials[a]
Less than 60 kg	500 mg	2
60 to 100 kg	750 mg	3
More than 100 kg	1000 mg	4

[a] Each vial provides 250 mg of abatacept for administration.

Subcutaneous Dosing Regimen

ORENCIA 125 mg in prefilled syringes should be administered by subcutaneous injection once weekly [*see Dosage and Administration (2.4)*] and may be initiated with or without an intravenous loading dose. For patients initiating therapy with an intravenous loading dose, ORENCIA should be initiated with a single intravenous infusion (as per body weight categories listed in Table 1), followed by the first 125 mg subcutaneous injection administered within a day of the intravenous infusion.

Patients transitioning from ORENCIA intravenous therapy to subcutaneous administration should administer the first subcutaneous dose instead of the next scheduled intravenous dose.

2.2 Polyarticular Juvenile Idiopathic Arthritis

For patients with juvenile idiopathic arthritis (JIA), ORENCIA may be administered as an intravenous infusion (6 years of age and older). Intravenous dosing has not been studied in patients younger than 6 years of age.

Intravenous Dosing Regimen

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 intravenously 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 intravenous 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.

Subcutaneous Dosing Regimen

Subcutaneous ORENCIA is not indicated for use in Polyarticular Juvenile Idiopathic Arthritis.

2.3 Adult Psoriatic Arthritis

For adult patients with psoriatic arthritis, ORENCIA may be administered as an intravenous infusion (IV) or a subcutaneous (SC) injection.

ORENCIA can be used with or without non-biologic DMARDs.

Intravenous Dosing Regimen

ORENCIA IV should be administered as a 30-minute intravenous infusion utilizing the weight range-based dosing specified in Table 1. Following the initial intravenous administration, an intravenous infusion should be given at 2 and 4 weeks after the first infusion and every 4 weeks thereafter.

Subcutaneous Dosing Regimen

ORENCIA SC 125 mg should be administered by subcutaneous injection once weekly without the need for an intravenous loading dose.

Patients switching from ORENCIA intravenous therapy to subcutaneous administration should administer the first subcutaneous dose instead of the next scheduled intravenous dose.

2.4 Preparation and Administration Instructions for Intravenous Infusion

Use aseptic technique.

ORENCIA for infusion 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.

1) Use 10 mL of Sterile Water for Injection, USP to reconstitute the ORENCIA powder. 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 to minimize foam formation, until the contents are completely dissolved. Do not shake. Avoid prolonged or vigorous agitation.

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). The solution should be clear to slightly opalescent and colorless to pale yellow. Do not use if opaque particles, discoloration, or other foreign particles are present.

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 ORENCIA vial 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 2ºC to 8ºC (36ºF to 46ºF) and protected from light before use. Discard the fully diluted solution if not administered within 24 hours.

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.

2.5 General Considerations for Subcutaneous Administration

ORENCIA prefilled syringes are intended for subcutaneous use only and are not intended for intravenous infusion.

ORENCIA prefilled syringes are intended for use under the guidance of a physician or healthcare practitioner. After proper training in subcutaneous injection technique, a patient or caregiver may inject with ORENCIA if a physician/healthcare practitioner determines that it is appropriate. Patients and caregivers should be instructed to follow the directions provided in the Instructions for Use for additional details on medication administration.

Inspect visually for particulate matter and discoloration prior to administration. Do not use ORENCIA prefilled syringes exhibiting particulate matter or discoloration. ORENCIA should be clear to slightly opalescent and colorless to pale yellow.

Patients using ORENCIA prefilled syringes for subcutaneous administration should be instructed to inject the full amount (1 mL), which provides 125 mg of ORENCIA, according to the directions provided in the Instructions for Use.

Injection sites should be rotated and injections should never be given into areas where the skin is tender, bruised, red, or hard.

4 CONTRAINDICATIONS

Hypersensitivity to abatacept or to any of the excipients listed in section 11 (Description).

5 WARNINGS AND PRECAUTIONS

5.1 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% vs. 43%) and serious infections (4.4% vs 0.8%) compared to patients treated with only TNF antagonists [see *Adverse Reactions (6.1)*]. These trials failed to demonstrate an important enhancement of efficacy with concomitant administration of ORENCIA with TNF antagonists; 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

In clinical trials of 2688 adult RA patients treated with intravenous ORENCIA, there were two cases (<0.1%) of anaphylaxis reactions. Other reactions 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 ORENCIA-treated patients in pJIA clinical trials, there was one case of a hypersensitivity reaction (0.5%) *[see Adverse Reactions (6.1,6.2)]*.

In postmarketing experience, fatal anaphylaxis following the first infusion of ORENCIA and life-threatening cases of angioedema have been reported. Angioedema has occurred as early as after the first dose of ORENCIA, but also has occurred with subsequent doses. Angioedema reactions have occurred within hours of administration and in some instances had a delayed onset (i.e., days).

Appropriate medical support measures for the treatment of hypersensitivity reactions should be available for immediate use in the event of a reaction. If an anaphylactic or other serious allergic reaction occurs, administration of intravenous or subcutaneous ORENCIA should be stopped

immediately with appropriate therapy instituted, and the use of ORENCIA should be permanently discontinued.

5.3 Infections

Serious infections, including sepsis and pneumonia, have been reported in patients receiving ORENCIA (serious infections were reported in 3% and 1.9% of RA patients treated with intravenous ORENCIA and placebo, respectively) *[see Adverse Reactions (6.1)]*. 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. A higher rate of serious infections has been observed in adult RA patients treated with concurrent TNF antagonists and ORENCIA compared to those treated with ORENCIA alone *[see Warnings and Precautions (5.1)]*.

Healthcare providers 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

Prior to initiating ORENCIA, patients should be screened for latent tuberculosis (TB) infection with a tuberculin skin test. ORENCIA has not been studied in patients with a positive TB screen, and the safety of ORENCIA in individuals with latent TB infection is unknown. Patients testing positive in TB 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

Prior to initiating ORENCIA in pediatric and adult patients, update vaccinations in accordance with current vaccination guidelines. ORENCIA-treated patients may receive current non-live vaccines. Live vaccines should not be given concurrently with ORENCIA or within 3 months after discontinuation. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving ORENCIA. Based on its mechanism of action, ORENCIA may blunt the effectiveness of some immunizations.

5.5 Use in Patients with Chronic Obstructive Pulmonary Disease (COPD)

In Study V, adult COPD patients treated with ORENCIA for RA developed adverse events more frequently than those treated with placebo, including COPD exacerbations, cough, rhonchi, and dyspnea. A greater percentage of patients treated with ORENCIA developed a serious adverse event compared to patients treated with placebo (27% vs 6%) *[see Clinical Studies (14.1) and Adverse Reactions (6.1)]*. Use of ORENCIA in patients with COPD should be undertaken with caution and such patients should be monitored for worsening of their respiratory status.

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.

In clinical trials in patients with adult RA, a higher rate of infections was seen in ORENCIA-treated patients compared to placebo-treated patients *[see Warnings and Precautions (5.3) and Adverse Reactions (6.1)]*. The impact of treatment with ORENCIA on the development and course of malignancies is not fully understood [see *Adverse Reactions (6.1)*]. There have been reports of malignancies, including skin cancer in patients receiving ORENCIA [see *Adverse Reactions (6.4)*]. Periodic skin examinations are recommended for all ORENCIA-treated patients, particularly those with risk factors for skin cancer.

6 ADVERSE REACTIONS

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.

6.1 Clinical Trials Experience in Adult Patients with RA and PsA

Adverse Reactions in Adult Patients with RA Treated with Intravenous ORENCIA

The data from placebo-controlled studies described herein reflect exposure to ORENCIA administered intravenously in patients with active RA (1955 patients with ORENCIA, 989 with placebo)(Studies I through VI) *[see Clinical Studies (14.1)]*. 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 antagonist (204 patients with ORENCIA, 134 with placebo).

The concomitant use of ORENCIA with a TNF antagonist is not recommended *[see Indications and Usage (1.3)]*. The majority of patients in RA clinical studies received one or more of the following concomitant medications with ORENCIA: methotrexate, nonsteroidal anti-

inflammatory drugs (NSAIDs), corticosteroids, TNF antagonist, 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 reactions 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%), 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%).

Most Common Adverse Reactions in Adult Patients with RA Treated with Intravenous ORENCIA

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

Table 2: Most Common Adverse Reactions* During Placebo-Controlled RA Studies of Intravenous ORENCIA

	Intravenous ORENCIA (n=1955)[a]	**Placebo (n=989)[b]**
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%

* Occurred in ≥3% patients and >1% more frequently in ORENCIA-treated patients.

[a] Includes 204 patients on concomitant biologic DMARDs (adalimumab, anakinra, etanercept, or infliximab).

[b] Includes 134 patients on concomitant biologic DMARDs (adalimumab, anakinra, etanercept, or infliximab).

Infections in Adult Patients with RA Treated with Intravenous ORENCIA

In the placebo-controlled trials in patients with RA, infections were reported in 54% of intravenous 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% 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 Adult Patients with RA Treated with Intravenous ORENCIA

In the placebo-controlled portions of the clinical trials (1955 patients treated for RA 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 cases, 0.2%) than placebo-treated patients (0 cases, 0%). In the cumulative intravenous ORENCIA clinical trials in patients with RA (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 (5.6)*]. The potential role of ORENCIA in the development of malignancies in humans is unknown.

Infusion-Related Reactions and Hypersensitivity Reactions in Adult Patients with RA Treated with Intravenous ORENCIA

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 (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.

In clinical trials of 2688 adult RA patients treated with intravenous ORENCIA, there were two cases (<0.1%) of anaphylaxis. Other reactions 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 Treated for RA with Intravenous ORENCIA

In Study V [see *Clinical Studies (14.1)*], there were 37 and 17 patients with chronic obstructive pulmonary disease (COPD) who were treated for RA with ORENCIA and placebo, respectively. The COPD patients treated with ORENCIA for RA 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)*].

Adverse Reactions in Methotrexate-Naive Patients with RA Treated with Intravenous ORENCIA

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

Adverse Reactions in Adult Patients with RA Treated with Subcutaneous or Intravenous ORENCIA

The data described below are derived from Study SC-1. Study SC-1 was a randomized, double-blind, double-dummy, non-inferiority study that compared the safety of ORENCIA administered subcutaneously or intravenously in 1457 patients with RA, who received background methotrexate, and experienced an inadequate response to methotrexate (MTX-IR) *[see Clinical Studies (14.1)]*. The adverse reaction profile in patients treated with subcutaneous ORENCIA was similar to the adverse reaction profile in patients treated with intravenous ORENCIA and consistent with intravenous ORENCIA administered in Studies I-VI.

Injection Site Reactions in Adult RA Patients Treated with Subcutaneous ORENCIA

The overall frequency of injection site reactions in Study SC-1 was 2.6% (19/736) and 2.5% (18/721) for the subcutaneous ORENCIA group and the subcutaneous placebo group (given intravenous ORENCIA), respectively *[see Clinical Studies (14.1)]*. All these injection site reactions (including hematoma, pruritus, and erythema) were mild (83%) to moderate (17%) in severity, and none necessitated drug discontinuation.

Adverse Reactions in Adult Patients with PsA Treated with Intravenous or Subcutaneous ORENCIA

The safety of ORENCIA was evaluated in 594 patients with PsA (341 patients on ORENCIA and 253 patients on placebo), in two randomized, double-blind, placebo-controlled trials *[see Clinical Studies (14.3)]*. Of the 341 patients who received ORENCIA, 128 patients received intravenous ORENCIA (PsA-I) and 213 patients received subcutaneous ORENCIA (PsA-II). The safety profile was comparable between ORENCIA given intravenously in Study PsA-I and ORENCIA given subcutaneously in Study PsA-II and also consistent with the safety profile of ORENCIA in patients with RA *[see Warnings and Precautions (5), Adverse Reactions (6.1, 6.2)]*.

6.2 Clinical Trials Experience in Patients with Polyarticular Juvenile Idiopathic Arthritis

Adverse Reactions in Patients with pJIA Treated with Intravenous ORENCIA

In general, the adverse events in pediatric patients with polyarticular JIA (pJIA) treated with intravenous ORENCIA were similar in frequency and type to those seen in adult patients with RA treated with intravenous ORENCIA *[see Warnings and Precautions (5) and Adverse Reactions (6)]*.

Study JIA-1 was a three-part study including an open-label extension that assessed the safety of intravenous ORENCIA in 190 pediatric patients, 6 to 17 years of age, with pJIA. 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 intravenous ORENCIA.

Of the 190 pediatric patients with pJIA treated with intravenous 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.

6.3 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other abatacept products may be misleading.

Immunogenicity in Adult Patients with RA Treated with Intravenous ORENCIA

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 intravenous ORENCIA. Thirty-four of 1993 (2%) 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 the subset analysis 9 of 154 (6%) patients that had discontinued intravenous ORENCIA treatment 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 anti-abatacept antibody development to clinical response or adverse events was observed.

Immunogenicity in Adult RA Patients Treated with Subcutaneous or Intravenous ORENCIA

Study SC-1 compared the immunogenicity to abatacept following subcutaneous or intravenous ORENCIA administration. The overall immunogenicity frequency to abatacept was 1% (8/725) and 2% (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 in Adult RA Patients Treated with Subcutaneous ORENCIA Monotherapy

Study SC-2 was conducted to determine the effect of subcutaneous monotherapy use of ORENCIA on immunogenicity (without an intravenous loading dose) in 100 RA patients, who had not previously received ORENCIA or other CTLA4Ig. Patients in this study received either subcutaneous ORENCIA plus methotrexate (n=51) or subcutaneous ORENCIA monotherapy (n=49). No patients in either group developed anti- abatacept antibodies after 4 months of treatment. The safety observed in this study was consistent with that observed in the other subcutaneous studies.

Immunogenicity in Adult RA Patients After Treatment, Withdrawal, and then Restart of Subcutaneous ORENCIA

Study SC-3 was conducted to investigate the immunogenicity in adult RA patients after treatment, withdrawal (three months) and restart of ORENCIA subcutaneous treatment (patients were treated concomitantly with methotrexate). 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 (0%) patients who continued to receive subcutaneous ORENCIA developed anti-abatacept antibodies compared to 7/73 (10%) of patients who had subcutaneous ORENCIA withdrawn during this period. Half of the patients who received 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 (3%) in the group who received subcutaneous ORENCIA throughout, and 2/73 (3%) 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 compared to those who remained on subcutaneous therapy, (these results occurred in those who received or did not receive an intravenous loading dose). The safety observed in this study was consistent with that observed in the other studies.

<u>Immunogenicity in Patients with pJIA Treated with Intravenous ORENCIA</u>

Antibodies directed against the entire abatacept molecule or to the CTLA-4 portion of abatacept were assessed by ELISA assays in patients with pJIA following repeated treatment with

intravenous 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.

6.4 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 with ORENCIA, the following adverse reactions have been identified :

- Vasculitis (including cutaneous vasculitis and leukocytoclastic vasculitis)
- New or worsening psoriasis
- Non-melanoma skin cancers (basal cell carcinoma and squamous cell carcinoma)
- Angioedema reactions [see Warnings and Precautions (5.2)]

During postmarketing experience with intravenous ORENCIA, systemic infusion reactions were similar to that seen in the clinical trial experience with intravenous ORENCIA with the exception of one case of fatal anaphylaxis *[see Warnings and Precautions (5.2)]*. Postmarketing reports of systemic injection reactions (e.g., pruritus, throat tightness, dyspnea) have occurred following the use of subcutaneous ORENCIA.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il

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 pyrroloquinoline quinone (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 intravenous 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.

ORENCIA for subcutaneous administration does not contain maltose; therefore, patients do not need to alter their glucose monitoring.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The data with ORENCIA use in pregnant women are insufficient to inform on drug-associated risk. In reproductive toxicology studies in rats and rabbits, no fetal malformations were observed with intravenous administration of ORENCIA during organogenesis at doses that produced exposures approximately 29 times the exposure at the maximum recommended human dose (MRHD) of 10 mg/kg month on an AUC basis. However, in a pre- and postnatal development study in rats, ORENCIA altered immune function in female rats at 11 times the MRHD on an AUC basis.

Data

Human Data

There are no adequate and well-controlled studies of ORENCIA use in pregnant women. The data with ORENCIA use in pregnant women are insufficient to inform on drug-associated risk.

Animal Data

Intravenous administration of abatacept during organogenesis to mice (10, 55, or 300 mg/kg/day), rats (10, 45, or 200 mg/kg/day), and rabbits (10, 45, or 200 mg/kg every 3 days) produced exposures in rats and rabbits that were approximately 29 times the MRHD on an AUC basis (at maternal doses of 200 mg/kg/day in rats and rabbits), and no embryotoxicity or fetal malformations were observed in any species.

In a study of pre- and postnatal development in rats (10, 45, or 200 mg/kg every 3 days from gestation day 6 through lactation day 21), alterations in immune function in female offspring, consisting of a 9-fold increase in T-cell dependent antibody response relative to controls on postnatal day (PND) 56 and thyroiditis in a single female pup on PND 112, occurred at approximately 11 times the MRHD on an AUC basis (at a maternal dose of 200 mg/kg). No adverse effects were observed at approximately 3 times the MRHD (a maternal dose of 45 mg/kg). It is not known if immunologic perturbations in rats are relevant indicators of a risk for development of autoimmune diseases in humans exposed *in utero* to abatacept. 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)*].

8.2 Lactation

Risk Summary

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

8.3 Pediatric Use

The safety and effectiveness of ORENCIA for reducing signs and symptoms in patients 6 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis (pJIA) have been established. Use of ORENCIA for this indication is supported by evidence from the following studies:

Intravenous Use: A randomized withdrawal efficacy, safety, and pharmacokinetic study of intravenous ORENCIA in 190 pediatric patients 6 to 17 years of age with pJIA *[see Clinical Pharmacology (12.3)*

and Clinical Studies (14.2)]. Given that population pharmacokinetic (PK) analyses (after intravenous ORENCIA administration) showed that clearance of abatacept increased with baseline body weight, intravenous ORENCIA is administered either weight-based or weight ranged based *[see Dosage and Administration (2.2)]*. Intravenous ORENCIA administration has not been studied in patients younger than 6 years of age.

ORENCIA IV lyophilized powder is not indicated for use in patients below the age of 6 years.

The safety and efficacy of ORENCIA in pediatric patients for uses other than pJIA have not been established.

Subcutaneous (SC) ORENCIA injection is not indicated for use in children (only for adults).

It is unknown if abatacept can cross the placenta into the fetus when a woman is treated with ORENCIA during pregnancy. Since abatacept is an immunomodulatory agent, the safety of administering live vaccines in infants exposed *in utero* to abatacept is unknown. Risk and benefits should be considered prior to vaccinating such infants.

Juvenile Animal Toxicity Data

A juvenile animal study conducted in rats dosed with abatacept from 4 to 94 days of age (prior to immune system maturity) showed an increase in the incidence of infections leading to death 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 contrast, 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 is unknown.

8.4 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 geriatric patients (patients aged 65 years of age and older) and younger adults, and other reported clinical experience has not identified differences in responses between geriatric patients and younger adults, but greater sensitivity of some geriatric patients cannot be ruled out. 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 geriatric population in general, caution should be used when treating geriatric patients.

9 OVERDOSAGE

Doses up to 50 mg/kg (5 times the maximum recommended dose) 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.

10 DESCRIPTION

Abatacept is a selective T cell costimulation modulator. 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 (abatacept) for injection is a sterile, white to off-white, preservative-free, lyophilized powder for reconstitution and dilution prior to intravenous infusion. Following reconstitution of the lyophilized powder with 10 mL of Sterile Water for Injection, USP, the reconstituted solution of ORENCIA is clear to slightly opalescent, colorless to pale yellow, with a concentration of 25 mg/mL and with a pH range of 7.2 to 7.8. Each single-dose vial of ORENCIA provides 262.5 mg abatacept, maltose monohydrate (525 mg), sodium Dihydrogen Phosphate Monohydrate (18.1 mg), sodium chloride (15.3 mg)., Hydrochloric acid (adjust pH to ~7.5), Sodium Hydroxide (adjust pH to ~7.5).

ORENCIA (abatacept) solution for injection for subcutaneous administration is supplied as a sterile, preservative-free, clear to slightly opalescent, colorless to pale-yellow solution with a pH range of 6.8 to 7.4for subcutaneous administration. ORENCIA injection is supplied as a single-dose prefilled syringe (See Table 3).

Table 3: Contents of ORENCIA Subcutaneous Injection

Presentation	**Active Ingredient Quantity and Label Volume**	**Inactive Ingredient Content**
ORENCIA injection 125 mg/mL prefilled syringe	125.875 mg of abatacept in 1.007 mL of solution	Sucrose 171.19 mg Poloxamer 188 8.056 mg Disodium Phosphate Anhydrous 0.844 mg Sodium Phosphate Monobasic Monohydrate 0.288 mg Water for Injection q.s. 1.007 ml

Unlike the lyophilized formulation for intravenous use, the ORENCIA solutions for subcutaneous administration contain no maltose.

11 CLINICAL PHARMACOLOGY

11.1 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, pJIA and PsA and are found in the synovium of patients with RA, pJIA and PsA.

In vitro, abatacept decreases T-cell proliferation and inhibits the production of the cytokines TNF alpha (TNFα), interferon-γ, 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-γ. The relationship of these biological response markers to the mechanisms by which ORENCIA exerts its clinical effects is unknown.

11.2 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 TNFα. The relationship of these biological response markers to the mechanisms by which ORENCIA exerts its clinical effects is unknown.

11.3 Pharmacokinetics

Healthy Adults and Adult RA - Intravenous Administration

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 of ORENCIA (see Table 4).

Table 4: Pharmacokinetic Parameters (Mean, Range) in Healthy Subjects and RA Patients After 10 mg/kg ORENCIA Intravenous Infusion(s)

PK Parameter	Healthy Subjects (After 10 mg/kg Single Dose) n=13	RA Patients (After 10 mg/kg Multiple Doses[a]) n=14
Peak Concentration (C_{max}) [mcg/mL]	292 (175-427)	295 (171-398)
Terminal half-life ($t_{1/2}$) [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 (Vss) [L/kg]	0.09 (0.06-0.13)	0.07 (0.02-0.13)

[a] Multiple intravenous infusions of ORENCIA 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_{max} 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 mcg/mL (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 methotrexate, NSAIDs, corticosteroids, and TNF antagonists 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.

Adult RA - Subcutaneous Administration

Abatacept exhibited linear pharmacokinetics following subcutaneous administration. The mean (range) for C_{min} and C_{max} at steady state observed after 85 days of treatment was 32.5 mcg/mL (6.6 to 113.8 mcg/mL) and 48.1 mcg/mL (9.8 to 132.4 mcg/mL), respectively. The bioavailability of abatacept following subcutaneous administration relative to intravenous administration was 79%. Mean estimates for systemic clearance (0.28 mL/h/kg), volume of distribution (0.11 L/kg), and

terminal half-life (14.3 days) were comparable between subcutaneous and intravenous administration.

Study SC-2 was conducted to determine the effect of subcutaneous monotherapy use of ORENCIA on immunogenicity (without an intravenous loading dose) in 100 RA patients *[see Adverse Reactions (6.3)]*.In this study, a mean trough concentration of 12.6 mcg/mL was achieved after 2 weeks of dosing.

Consistent with the intravenous data, population pharmacokinetic analyses for subcutaneous ORENCIA in RA patients revealed that there was a trend toward higher clearance of abatacept with increasing body weight *[see Dosage and Administration (2.1)]*. Age and gender (when corrected for body weight) did not affect apparent clearance. Concomitant medication, such as methotrexate, corticosteroids, and NSAIDs, did not influence abatacept apparent clearance.

Polyarticular Juvenile Idiopathic Arthritis - Intravenous Administration

In Study JIA-1 among patients 6 to 17 years of age, the mean (range) steady state serum peak and trough concentrations of abatacept were 217 mcg/mL (57 to 700 mcg/mL) and 11.9 mcg/mL (0.15 to 44.6 mcg/mL)*[see Clinical Studies (14.2)]*. Population pharmacokinetic analyses of the serum concentration data showed that clearance of abatacept increased with baseline body weight *[see Dosage and Administration (2.2)]*. The estimated mean (range) clearance of abatacept in the juvenile idiopathic arthritis patients was 0.4 mL/h/kg (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.

Adult Psoriatic Arthritis - Intravenous and Subcutaneous Administration

In Study PsA-I, a dose ranging study, intravenous ORENCIA was administered at 3 mg/kg, weight range-based dosing: 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, or doses of 30 mg/kg on Days 1 and 15 followed by weight range-based dosing *[see Clinical Studies (14.3)]*. Following monthly intravenous ORENCIA administration, abatacept showed linear PK over the dose range in this study. At the weight-range –based dosing (see above), the steady state of abatacept was reached by Day 57 and the geometric mean (CV%) trough concentration (Cmin) was 24.3 mcg/mL (40.8%) at Day 169. In Study PsA-II following weekly subcutaneous administration of ORENCIA at 125 mg, the steady state of abatacept was reached at Day 57 and the geometric mean (CV%) Cmin was 25.6 mcg/mL (47.7%) at Day 169.

Consistent with the RA results, population pharmacokinetic analyses for abatacept in PsA patients revealed that there was a trend toward higher clearance (L/h) of abatacept with increasing body weight *[see Dosage and Administration (2.3)]*. In addition, relative to the RA patients with the

same body weight, abatacept clearance in PsA patients was approximately 8% lower, resulting in higher abatacept exposures in patients with PsA. This slight difference in exposures, however, is not considered to be clinically meaningful.

12 NONCLINICAL TOXICOLOGY

12.1 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).

12.2 Animal Toxicology and/or Pharmacology

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.

13 CLINICAL STUDIES

13.1 Adult Rheumatoid Arthritis

Description of Clinical Studies of Intravenous ORENCIA for the Treatment of Patients with RA

The efficacy and safety of ORENCIA for intravenous administration were assessed in six randomized, double-blind, controlled studies (five placebo-controlled and one active-controlled) in patients ≥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, and 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 in Studies I, II, III, IV, and VI.

- 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 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 of ORENCIA was assessed in patients with an inadequate response to a TNF antagonist, with the TNF antagonist 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 methotrexate-naive patients with RA of less than 2 years disease duration. In Study VI, patients previously naive to methotrexate were randomized to receive ORENCIA plus methotrexate or methotrexate 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.

Description of Clinical Studies of Subcutaneous or Intravenous ORENCIA for the Treatment of Patients with Adult RA

The efficacy of ORENCIA for subcutaneous administration were assessed in Study SC-1, which was a randomized, double-blind, double-dummy, non-inferiority study that compared ORENCIA administered subcutaneously to ORENCIA administered intravenously in 1457 patients with moderate to severely active RA, receiving background methotrexate (MTX), and experiencing an inadequate response to methotrexate (MTX-IR). In Study SC-1, patients were randomized with stratification by body weight (<60 kg, 60 to 100 kg, >100 kg) to receive (1) ORENCIA 125 mg subcutaneous injections weekly, after a single intravenous loading dose of ORENCIA based on body weight or (2) ORENCIA intravenously on Days 1, 15, 29, and every four weeks thereafter. Subjects continued taking their current dose of MTX from the day of randomization.

Clinical Response in Adult RA Patients

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

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 5). 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.

In Study SC-1, the main outcome measure was ACR 20 at 6 months. The pre-specified non-inferiority margin was a treatment difference of −7.5%. As shown in Table 5, the study demonstrated non-inferiority of ORENCIA administered subcutaneously to intravenous infusions of ORENCIA with respect to ACR 20 responses up to 6 months of treatment. ACR 50 and 70 responses are also shown in Table 5. No major differences in ACR responses were observed

between intravenous and subcutaneous treatment groups in subgroups based on weight categories (less than 60 kg, 60 to 100 kg, and more than 100 kg; data not shown).

Table 5: Clinical Responses in Controlled Trials in Patients with RA

	Percent of Patients									
	Intravenous Administration								**Subcutaneous or Intravenous Administration**	
	Inadequate Response to DMARDs		**Inadequate Response to Methotrexate (MTX)**		**Inadequate Response to TNF Antagonists**		**MTX-Naive**		**Inadequate Response to MTX**	
	Study I		**Study III**		**Study IV**		**Study VI**		**Study SC-1**	
Response Rate	ORN[a] n=32	PBO n=32	ORN[b] +MTX n=424	PBO +MTX n=214	ORN[b] + DMARDs n=256	PBO + DMARDs n=133	ORN[b] +MTX n=256	PBO +MTX n=253	ORN[e] SC +MTX n=693	ORN[e] IV +MTX n=678
ACR 20										
Month 3	53%	31%	62%‡	37%	46%‡	18%	64%*	53%	68%	69%
Month 6	NA	NA	68%‡	40%	50%‡	20%	75%†	62%	76%§	76%
Month 12	NA	NA	73%‡	40%	NA	NA	76%‡	62%	NA	NA
ACR 50										
Month 3	16%	6%	32%‡	8%	18%†	6%	40%‡	23%	33%	39%
Month 6	NA	NA	40%‡	17%	20%‡	4%	53%‡	38%	52%	50%
Month 12	NA	NA	48%‡	18%	NA	NA	57%‡	42%	NA	NA
ACR 70										
Month 3	6%	0	13%‡	3%	6%*	1%	19%†	10%	13%	16%
Month 6	NA	NA	20%‡	7%	10%†	2%	32%†	20%	26%	25%
Month 12	NA	NA	29%‡	6%	NA	NA	43%‡	27%	NA	NA
Major Clinical Response[c]	NA	NA	14%‡	2%	NA	NA	27%‡	12%	NA	NA
DAS28-CRP <2.6[d]										
Month 12	NA	NA	NA	NA	NA	NA	41%‡	23%	NA	NA

* 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.

§ 95% CI: −4.2, 4.8 (based on prespecified margin for non-inferiority of −7.5%).

[a] 10 mg/kg.

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

[c] Major clinical response is defined as achieving an ACR 70 response for a continuous 6-month period.

[d] Refer to text for additional description of remaining joint activity.

[e] Per protocol data is presented in table. For ITT; n=736, 721 for SC and IV ORENCIA, respectively.

The results of the components of the ACR response criteria for Studies III, IV, and SC-1 are shown in Table 6 (results at Baseline [BL] and 6 months [6 M]). 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 6: Components of ACR Responses at 6 Months in Adult Patients with RA

	Intravenous Administration								**Subcutaneous or Intravenous Administration**			
	Inadequate Response to MTX				**Inadequate Response to TNF Antagonists**				**Inadequate Response to MTX**			
	Study III				**Study IV**				**Study SC-1[c]**			
	ORN +MTX n=424		PBO +MTX n=214		ORN +DMARDs n=256		PBO +DMARDs n=133		ORN SC +MTX n=693		ORN IV +MTX n=678	
Component (median)	BL	6 M	BL	6 M	BL	6 M	BL	6 M	BL	6 M	BL	6 M
Number of tender joints (0-68)	28	7‡	31	14	30	13‡	31	24	27	5	27	6
Number of swollen joints (0-66)	19	5‡	20	11	21	10‡	20	14	18	4	18	3
Pain[a]	67	27‡	70	50	73	43†	74	64	71	25	70	28
Patient global assessment[a]	66	29‡	64	48	71	44‡	73	63	70	26	68	27
Disability index[b]	1.75	1.13‡	1.75	1.38	1.88	1.38‡	2.00	1.75	1.88	1.00	1.75	1.00

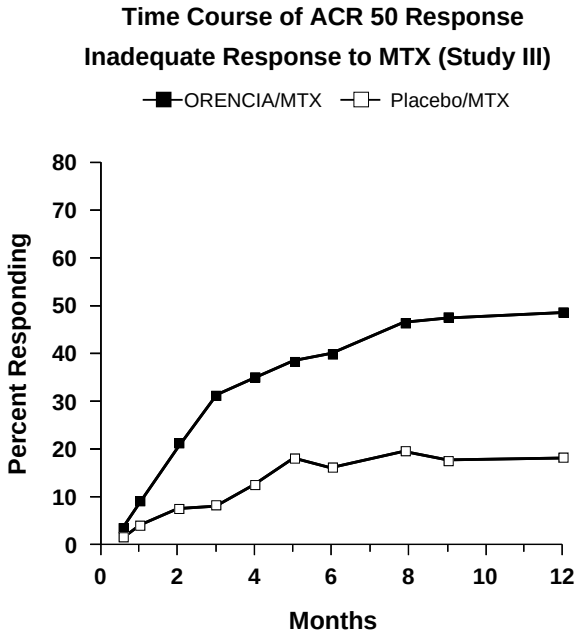
Table 6: Components of ACR Responses at 6 Months in Adult Patients with RA

	Intravenous Administration								Subcutaneous or Intravenous Administration			
	Inadequate Response to MTX				Inadequate Response to TNF Antagonists				Inadequate Response to MTX			
Physician global assessment[a]	69	21‡	68	40	71	32‡	69	54	65	16	65	15
CRP (mg/dL)	2.2	0.9‡	2.1	1.8	3.4	1.3‡	2.8	2.3	1.6	0.7	1.8	0.7

† p<0.01, ORENCIA (ORN) vs placebo (PBO), based on mean percent change from baseline.
‡ p<0.001, ORENCIA vs placebo, based on mean percent change from baseline.
[a] Visual analog scale: 0 = best, 100 = worst.
[b] Health Assessment Questionnaire: 0 = best, 3 = worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.
[c] SC-1 is a non-inferiority study. Per protocol data is presented in table.

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.

The percent of patients achieving the ACR 50 response for Study SC-1 in the ORENCIA subcutaneous (SC) and intravenous (IV) treatment arms at each treatment visit was as follows: Day 15—SC 3%, IV 5%; Day 29—SC 11%, IV 14%; Day 57—SC 24%, IV 30%; Day 85—SC 33%, IV 38%; Day 113—SC 39%, IV 41%; Day 141—SC 46%, IV 47%; Day 169—SC 51%, IV 50%.

Radiographic Response in Adult RA Patients

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 7.

Table 7: Mean Radiographic Changes in Study III[a] and Study VI[b]

Parameter	ORENCIA/MTX	Placebo/MTX	Differences	P-value[d]
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[c]	-	-
ES	0.23	0.22[c]	-	-
JSN score	0.25	0.51[c]	-	-
Study VI				
First Year				
TSS	0.6	1.1	0.5	0.04

[a] Patients with an inadequate response to MTX.
[b] MTX-naive patients.
[c] Patients received 1 year of placebo/MTX followed by 1 year of ORENCIA/MTX.
[d] 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 7, 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 in Adult RA Patients

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. In Study SC-1, improvement from baseline as measured by HAQ-DI at 6 months and over time was similar between subcutaneous and intravenous ORENCIA administration. The results from Studies II and III are shown in Table 8. 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 8: Mean Improvement from Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) in Adult Patients with RA

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

*** p<0.001, ORENCIA vs placebo.

[a] 10 mg/kg.

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

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

[d] 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).

13.2 Polyarticular Juvenile Idiopathic Arthritis

Polyarticular Juvenile Idiopathic Arthritis- Intravenous Administration

The safety and efficacy of ORENCIA with intravenous administration were assessed in Study JIA-1, a three-part study including an open-label extension in pediatric patients with polyarticular juvenile idiopathic arthritis (pJIA). Patients 6 to 17 years of age (n=190) with moderately to severely active pJIA 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 JIA subtypes that at disease onset included oligoarticular (16%), polyarticular (64%; 20% were rheumatoid factor positive), and systemic JIA without systemic manifestations (20%). At study

entry, 74% of patients were receiving MTX (mean dose, 13.2 mg/m^2 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 ≥30% improvement in at least 3 of the 6 JIA core set variables and ≥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 ≥30% worsening in at least 3 of the 6 JIA core set variables with ≥30% improvement in not more than 1 of the 6 JIA core set variables; ≥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 ≥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 (intravenous) 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 intravenous ORENCIA was less than one-third than that for patients withdrawn from intravenous ORENCIA treatment (hazard ratio=0.31, 95% CI [0.16, 0.59]). Among patients who received intravenous 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.

13.3 Adult Psoriatic Arthritis

The efficacy of ORENCIA was assessed in 594 adult patients (18 years and older) with psoriatic arthritis (PsA), in two randomized, double-blind, placebo-controlled studies (Studies PsA-I and PsA-II). Patients had active PsA(≥3 swollen joints and ≥3 tender joints) despite prior treatment with DMARD therapy and had one qualifying psoriatic skin lesion of at least 2 cm in diameter. In PsA-I and PsA-II, 37% and 61% of patients, respectively, were treated with TNF antagonists previously.

During the initial 24-week, double blind period of Study PsA-I, 170 patients were randomized to receive one of four intravenous treatments on Days 1, 15, 29, and then every 28 days (there was no escape during the 24-week period):

- Placebo
- ORENCIA 3 mg/kg,
- ORENCIA 500 mg for patients weighing less than 60 kg, ORENCIA 750 mg for patients weighing 60 to 100 kg, and ORENCIA 1000 mg for patients weighing greater than 100 kg (weight-range-based dosing), or
- ORENCIA 30 mg/kg on Days 1 and 15 followed by weight range-based ORENCIA dosing (i.e., 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).

After the 24-week double blind period in Study PsA-I, patients received open-label intravenous ORENCIA every 28 days.

Patients were allowed to receive stable doses of concomitant MTX, low dose corticosteroids (equivalent to ≤10 mg of prednisone) and/or NSAIDs during the trial. At enrollment, approximately 60% of patients were receiving MTX. At baseline, the mean (SD) CRP for ORENCIA IV was 17 mg/L (33.0) and mean number (SD) of tender joints and swollen joints was 22.2 (14.3) and 10.9 (7.6), respectively.

In PsA-II, 424 patients were randomized 1:1 to receive weekly doses of subcutaneous placebo or ORENCIA 125 mg without a loading dose for 24 weeks-in a double-blind manner, followed by open-label subcutaneous ORENCIA 125 mg weekly. Patients were allowed to receive stable doses of concomitant MTX, sulfasalazine, leflunomide, hydroxychloroquine, low dose corticosteroids (equivalent to ≤10 mg of prednisone) and/or NSAIDs during the trial. At randomization, 60% of patients were receiving MTX. The baseline disease characteristics included presence of joint erosion on X-rays in 84% (341/407) with a mean (SD) PsA-modified Sharp van der Heijde erosion score (SHS) of 10.8 (24.2), elevated serum C reactive protein (CRP) in 66% [277/421]) with a mean (SD) of 14.1 mg/L (25.9), and polyarticular disease in 98% (416/424) of patients with a mean number (SD) of tender joints and swollen joints of 20.2 (13.3) and 11.6 (7.5), respectively. Patients who had not achieved at least a 20% improvement from baseline in their swollen and tender joint counts by Week 16 escaped to open-label subcutaneous ORENCIA 125 mg weekly.

The primary endpoint for both PsA-I and PsA-II was the proportion of patients achieving ACR 20 response at Week 24 (Day 169).

Clinical Response in Adults with PsA

A greater proportion of adult patients with PsA achieved an ACR20 response after treatment with intravenous ORENCIA (weight range-based dosing as described above) compared to placebo in Study PsA-I and a greater proportion of adult patients with PsA achieved an ACR20 response after treatment with subcutaneous 125 mg compared to placebo in Study PsA-II at Week 24. Responses

were seen regardless of prior TNF antagonist treatment and regardless of concomitant non-biologic DMARD treatment. The percent of patients achieving ACR 20, 50, or 70 responses in Studies PsA-I and PsA-II are presented in Table 9 below

Table 9: Proportion of Patients With ACR Responses at Week 24 in Studies PsA-I and PsA-II[a]

	PsA-I		PsA-II	
	ORENCIA Weight-Range-Based Intravenous Dosing[b]	**Placebo**	**ORENCIA 125 mg Subcutaneous**	**Placebo**
	N=40	**N=42**	**N=213**	**N=211**
ACR 20	47.5%*	19.0%	39.4%*	22.3%
ACR 50	25.0%	2.4%	19.2%	12.3%
ACR 70	12.5%	0%	10.3%	6.6%

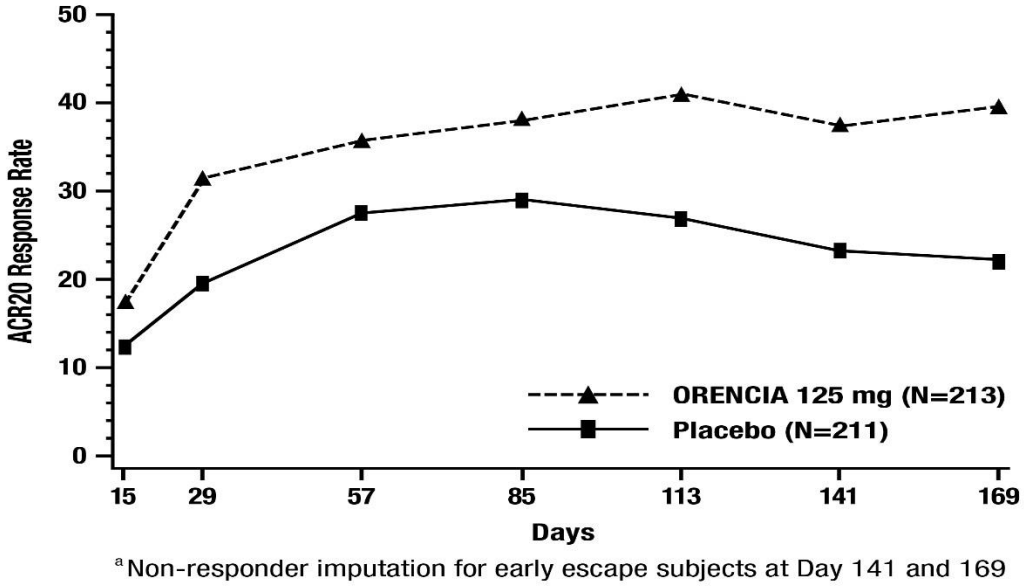
* $p<0.05$ versus placebo.

[a] Patients who had less than 20% improvement in tender or swollen joint counts at Week 16 met escape criteria and were considered non-responders.

[b] Weight range-based intravenous dosing: ORENCIA 500 mg for patients weighing less than 60 kg, ORENCIA 750 mg for patients weighing 60 to 100 kg, and ORENCIA 1000 mg for patients weighing greater than 100 kg.

The percentage of patients in PsA-II achieving ACR20 response through Week 24 is shown below in Figure 2.

Figure 2: Percent of Patients Achieving ACR20 Response[a] in PsA-II Study Through Week 24 (Day 169)



[a] Non-responder imputation for early escape subjects at Day 141 and 169

Results were generally consistent across the ACR components in Study PsA-I and PsA-II.

Improvements in enthesitis and dactylitis were seen with ORENCIA treatment at Week 24 in both PsA-I and PsA-II.

Physical Function Response in Adults with PsA

In study PsA-I, there was a higher proportion of patients with at least a 0.30 decrease from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) score at Week 24, with an estimated difference for ORENCIA weight range-based dosing as described above (45%) vs. placebo (19%) of 26.1 (95% confidence interval: 6.8, 45.5). In study PsA-II, the proportion of patients with at least a 0.35 decrease from baseline in HAQ-DI on ORENCIA was 31%, as compared to 24% on placebo (estimated difference: 7%; 95% confidence interval: -1%, 16%). There was a higher adjusted mean change from baseline in HAQ-DI on ORENCIA (-0.33) vs. placebo (-0.20) at Week 24, with an estimated difference of -0.13 (95% confidence interval: -0.25, -0.01).

14 HOW SUPPLIED/STORAGE AND HANDLING

For Intravenous Infusion

ORENCIA® (abatacept) for injection is a white to off-white lyophilized powder for intravenous infusion after reconstitution and dilution. It is supplied as an individually packaged, single-dose

vial (one may use less than the full contents of the vial or use more than one vial) with a silicone-free disposable syringe, providing 250 mg of abatacept.

For Subcutaneous Use

ORENCIA (abatacept) injection is a clear to slightly opalescent, colorless to pale yellow solution for subcutaneous administration.

Prefilled Syringe

ORENCIA (abatacept) injection, 125 mg/mL, is supplied as a single-dose disposable prefilled glass syringe with BD UltraSafe Passive™ needle guard and flange extenders. The Type I glass syringe has a coated stopper and fixed stainless steel needle (5 bevel, 29-gauge thin wall, ½-inch needle) covered with a rigid needle shield. The prefilled syringe provides ORENCIA in the following package:

(125 mg/ml): pack of 4 syringes with a passive needle safety guard.

Storage

Refrigerate ORENCIA lyophilized powder supplied in a vial at 2°C to 8°C (36°F to 46°F) . Do not use beyond the expiration date on the vial. Protect the vials from light by storing in the original package until time of use.

Refrigerate ORENCIA solution supplied in a prefilled syringe at 2°C to 8°C (36°F to 46°F). Do not use beyond the expiration date on the prefilled syringe. Protect from light by storing in the original package until time of use. Do not allow the prefilled syringe to freeze.

The expiry date of the product is indicated on the packaging materials.

MANUFACTURER

ORENCIA 125mg SC: Bristol-Myers Squibb Holdings Pharma, Ltd., Liability company, Manati, Puerto Rico, USA.

ORENCIA 250mg IV: Bristol-Myers Squibb Company, Princeton, New Jersey, 08543, USA.

LICENSE HOLDER

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REGISTRATION NUMBER

Orencia 125 mg SC 149-54-33788-00

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