Subcutaneous Use for Adult PsA (2.3)

- Administer 125 mg by subcutaneous injection once weekly without an intravenous loading dose.
- Patients switching from intravenous use to subcutaneous use, administer first subcutaneous dose instead of next scheduled intravenous dose.

Intravenous Use for prophylaxis of aGVHD (2.4)

- For patients 6 years and older, administer at a 10 mg/kg dose (maximum dose 1,000 mg) as a 60-minute infusion on the day before transplantation, followed by a dose on Day 5, 14, and 28 after transplant (2.4).
- For patients 2 to less than 6 years old, administer a 15 mg/kg dose as a 60-minute infusion on the day before transplantation, followed by a 12 mg/kg dose as a 60-minute infusion on Day 5, 14, and 28 after transplant (2.4).

Preparation and Administration Instructions

- Administer as a 30-minute intravenous infusion for RA, pJIA, and PsA (2.5).
- Administer as a 60-minute intravenous infusion for aGVHD prophylaxis (2.5).
- See the Full Prescribing Information for preparation and administration instructions for intravenous infusion and recommendations for subcutaneous use (2.5, 2.6). Prepare ORENCIA (abatacept) using only the silicone-free disposable syringe (2.5).
ORENCIA® (abatacept) is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis.

2 DOSE AND ADMINISTRATION

2.1 Dosage in Adult Rheumatoid Arthritis

For adult patients with RA, administer as an intravenous infusion or as a subcutaneous injection. ORENCIA may be used as monotherapy or concomitantly with disease-modifying antirheumatic drugs (DMARDs) other than JAK inhibitors or bDMARDs (e.g., TNF antagonists).

Intravenous Dosing Regimen

Reconstitute ORENCIA lyophilized powder and administer after dilution [see Dosage and Administration (2.5)] as a 30-minute intravenous infusion utilizing the weight range-based dosing as specified in Table 1. Following the initial intravenous administration, administer an intravenous infusion at 2 and 4 weeks and every 4 weeks thereafter.

<table>
<thead>
<tr>
<th>Body Weight of Adult Patient</th>
<th>Dose</th>
<th>Number of Vials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 60 kg</td>
<td>500 mg</td>
<td>2</td>
</tr>
<tr>
<td>60 to 100 kg</td>
<td>750 mg</td>
<td>3</td>
</tr>
<tr>
<td>More than 100 kg</td>
<td>1,000 mg</td>
<td>4</td>
</tr>
</tbody>
</table>

* Each vial provides 250 mg of abatacept for administration.

Subcutaneous Dosing Regimen

Prior to the first subcutaneous dose, may administer an optional loading dose as a single intravenous infusion (as per body weight categories in Table 1), if an intravenous loading dose is used, administer the first subcutaneous injection within one day of the infusion. Administer ORENCIA 125 mg in prefilled syringes or in ORENCIA ClickJect™ autoinjector by subcutaneous injection once weekly [see Dosage and Administration (2.6)].

For patients switching from ORENCIA intravenous therapy to subcutaneous administration, administer the first subcutaneous dose instead of the next scheduled intravenous dose.

1.2 Polyarticular Juvenile Idiopathic Arthritis

ORENCIA is indicated for the treatment of patients 2 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis.

1.3 Adult Psoriatic Arthritis

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

1.4 Prophylaxis for Acute Graft versus Host Disease

ORENCIA is indicated for the prophylaxis of acute graft versus host disease (aGvHD), in combination with a calcineurin inhibitor and methotrexate, in adults and pediatric patients 2 years of age and older undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele–mismatched unrelated donor.

1.5 Limitations of Use

The concomitant use of ORENCIA with other potent immunosuppressants [e.g., biologic disease-modifying antirheumatic drugs (bDMARDs), Janus kinase (JAK) inhibitors] is not recommended.

2 USE IN SPECIFIC POPULATIONS

2.1 Pregnancy

ORENCIA is not recommended in pregnant women and should only be given to pregnant women if the potential benefits outweigh the potential risks.

2.2 Lactation

It is not known if ORENCIA is present in human milk. Because many drugs are excreted in human milk, caution should be exercised when ORENCIA is administered to a nursing woman.

2.3 Neonates and Pediatric Patients

Use of ORENCIA in pediatric patients has not been tested.

2.3.1 Pediatric Patients Aged 2 Years and Older

<table>
<thead>
<tr>
<th>Body Weight of Pediatric Patient</th>
<th>Dose (once weekly)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 to less than 25 kg</td>
<td>50 mg</td>
</tr>
<tr>
<td>25 to less than 50 kg</td>
<td>87.5 mg</td>
</tr>
<tr>
<td>50 kg or more</td>
<td>125 mg</td>
</tr>
</tbody>
</table>

PJIA patients may self-inject with ORENCIA or the patient’s caregiver may administer ORENCIA if both the healthcare practitioner and the parent/legal guardian determine it is appropriate. The ability of pediatric patients to self-inject with the autoinjector has not been tested.

2.4 Dosage in Polyarticular Juvenile Idiopathic Arthritis

For patients with polyarticular juvenile idiopathic arthritis (pJIA), may administer ORENCIA (abatacept) as an intravenous infusion (only patients 6 years of age and older) or a subcutaneous injection (only patients 2 years of age and older) [see Use in Specific Populations (8.4)]. ORENCIA may be used as monotherapy or concomitantly with methotrexate.

Intravenous Dosing Regimen

Administer ORENCIA as a 30-minute intravenous infusion based on body weight [see Dosage and Administration (2.5)]:

- If less than 75 kg, administer a dose of 10 mg/kg.
- If 75 kg or greater, administer as per the recommendations in Table 1 (follow the adult intravenous dosing regimen), not to exceed a maximum dose of 1,000 mg.

Subcutaneous Dosing Regimen

Administer ORENCIA for subcutaneous injection, without an intravenous loading dose, utilizing the weight range-based dosing as specified in Table 2 [see Dosage and Administration (2.6)]. Subsequently administer once weekly.

Table 2: Dose of ORENCIA for Subcutaneous Administration in Patients 2 Years of Age and Older with JIA

<table>
<thead>
<tr>
<th>Body Weight of Pediatric Patient</th>
<th>Dose (once weekly)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 to less than 25 kg</td>
<td>50 mg</td>
</tr>
<tr>
<td>25 to less than 50 kg</td>
<td>87.5 mg</td>
</tr>
<tr>
<td>50 kg or more</td>
<td>125 mg</td>
</tr>
</tbody>
</table>

2.4.1 Adult Psoriatic Arthritis

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

Intravenous Dosing Regimen

Administer ORENCIA as a 30-minute intravenous infusion utilizing the weight range-based dosing as specified in Table 1 [see Dosage and Administration (2.5)]. Subsequently administer once weekly.

Subcutaneous Dosing Regimen

Administer ORENCIA 125 mg of ORENCIA subcutaneously once weekly (no intravenous loading dose is needed) [see Dosage and Administration (2.6)].

For patients switching from ORENCIA intravenous infusions to subcutaneous administration, administer the first subcutaneous dose instead of the next scheduled intravenous dose.

2.4.2 Adult Chronic Hematopoietic Stem Cell Transplantation

Administer ORENCIA 125 mg in prefilled syringes or in ORENCIA ClickJect™ autoinjector by subcutaneous injection once weekly [see Dosage and Administration (2.6)].

Subcutaneous Dosing Regimen

Administer 125 mg of ORENCIA subcutaneously once weekly (no intravenous loading dose is needed) [see Dosage and Administration (2.6)].

Antiviral Prophylactic Treatment

Before administering ORENCIA, administer recommended antiviral prophylactic treatment for Epstein-Barr Virus (EBV) reactivation, and continue for six months following HSCT.

2.4.3 Moderate to Severe Acute Graft-versus-Host Disease

Administer ORENCIA 125 mg in prefilled syringes or in ORENCIA ClickJect™ autoinjector by subcutaneous injection once weekly (no intravenous loading dose) [see Dosage and Administration (2.6)].

Subcutaneous Dosing Regimen

Administer 125 mg of ORENCIA subcutaneously once weekly (no intravenous loading dose is needed) [see Dosage and Administration (2.6)].

For patients switching from ORENCIA intravenous infusions to subcutaneous administration, administer the first subcutaneous dose instead of the next scheduled intravenous dose.

2.4.4 Severe Acute Graft-versus-Host Disease

For patients with severe acute graft-versus-host disease (severe aGvHD), may administer ORENCIA (abatacept) as an intravenous infusion (only patients 6 years of age and older) or a subcutaneous injection (only patients 2 years of age and older) [see Use in Specific Populations (8.4)]. ORENCIA may be used as monotherapy or concomitantly with methotrexate.

Intravenous Dosing Regimen

Administer ORENCIA as a 30-minute intravenous infusion based on body weight [see Dosage and Administration (2.5)]:

- If less than 75 kg, administer a dose of 10 mg/kg.
- If 75 kg or greater, administer as per the recommendations in Table 1 (follow the adult intravenous dosing regimen), not to exceed a maximum dose of 1,000 mg.

Subcutaneous Dosing Regimen

Administer ORENCIA for subcutaneous injection, without an intravenous loading dose, utilizing the weight range-based dosing as specified in Table 2 [see Dosage and Administration (2.6)]. Subsequently administer once weekly.

Table 2: Dose of ORENCIA for Subcutaneous Administration in Patients 2 Years of Age and Older with JIA

<table>
<thead>
<tr>
<th>Body Weight of Pediatric Patient</th>
<th>Dose (once weekly)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 to less than 25 kg</td>
<td>50 mg</td>
</tr>
<tr>
<td>25 to less than 50 kg</td>
<td>87.5 mg</td>
</tr>
<tr>
<td>50 kg or more</td>
<td>125 mg</td>
</tr>
</tbody>
</table>

PJA patients may self-inject with ORENCIA or the patient’s caregiver may administer ORENCIA if both the healthcare practitioner and the parent/legal guardian determines it is appropriate. The ability of pediatric patients to self-inject with the autoinjector has not been tested.
ORENCIA® (abatacept)

In addition, consider prophylactic antivirals for Cytomegalovirus (CMV) infection/reactivation during treatment and for six months following HSCT [see Warnings and Precautions (5.7)].

2.5 Preparation and Administration Instructions for Intravenous Infusion

Calculate the ORENCIA dose, the total volume of reconstituted solution required, and the number of ORENCIA vials needed. For a full dose, less than the full contents of one vial or more than one vial may be needed. Using aseptic technique, reconstitute, dilute, and then administer ORENCIA as follows:

Reconstitution

1) Use the vial only if the vacuum is present.
2) Reconstitute each vial of supplied ORENCIA lyophilized powder (each vial supplies 250 mg of abatacept) with 10 mL of Sterile Water for Injection, USP (direct the stream toward the inside wall of the vial) to obtain a concentration of 25 mg/mL. Use only the provided silicone-free syringe with an 18- to 21-gauge needle:
   a. If the ORENCIA lyophilized powder is accidently reconstituted using a siliconized syringe, the solution may develop a few translucent particles (discard any solutions prepared using siliconized syringes).
   b. If the silicone-free disposable syringe is dropped or becomes contaminated, use a new silicone-free disposable syringe. To obtain new silicone-free syringes, contact Bristol-Myers Squibb at 1-800-ORENCIA.
3) Gently swirl the vial to minimize foam formation, until the contents are completely dissolved. Do not shake. Avoid prolonged or vigorous agitation.
4) Upon complete dissolution of the lyophilized powder, vent the vial with a needle to dissipate any foam that may be present.
5) Visually inspect the reconstituted solution (the solution should be clear and colorless to pale yellow). Do not use if opaque particles, discoloration, or other foreign particles are present.
6) Repeat steps 2) through 5) if two, three, or four vials are needed for a dose (see Table 1).

Dilution

7) Must further dilute the reconstituted ORENCIA solution to 100 mL as follows:
   a. From a 100 mL infusion bag or bottle of 0.9% Sodium Chloride Injection, USP, withdraw a volume equal to the volume of the reconstituted ORENCIA solution required for the patient’s dose.
   b. Slowly add the reconstituted ORENCIA solution(s) into the infusion bag or bottle using the silicone-free disposable syringe provided with each vial.
   c. 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 abatacept added, but will be no more than 10 mg/mL. Immediately discard any unused portion in the ORENCIA vial.

Administration

8) Prior to administration, visually inspect the ORENCIA diluted solution for particulate matter and discoloration. Discard the diluted solution if any particulate matter or discoloration is observed.
9) Using an infusion set and a sterile, non-pyrogenic, low-protein-binding filter (pore size of 0.2 µm to 1.2 µm), administer the entire diluted ORENCIA solution over:
   • 30 minutes for RA, pJIA, and PsA
   • 60 minutes for aGVHD prophylaxis
10) Must complete the infusion of the diluted ORENCIA solution within 24 hours of reconstitution of the ORENCIA vial.
   Do not infuse ORENCIA 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 drugs.

Storage of Diluted ORENCIA Solution

May store the diluted ORENCIA solution at room temperature or refrigerate at 2°C to 8°C (36°F to 46°F) up to 24 hours before use. Discard the diluted solution if not administered within 24 hours.

2.6 Recommendations for Subcutaneous Administration

ORENCIA prefilled syringes and ORENCIA ClickJect autoinjectors are intended for:
   • subcutaneous use only and are not intended for intravenous infusion
   • use under the guidance of a healthcare practitioner.

ORENCIA® (abatacept)

After proper training in subcutaneous injection technique, a patient or the patient’s caregiver may administer a subcutaneous injection of ORENCIA (ClickJect autoinjector or prefilled syringes) if a healthcare practitioner determines that it is appropriate. Instruct patients and/or caregivers to follow the directions provided in the Instructions for Use for additional details on administration. Specifically instruct them to inject the full amount (which provides the proper dose of ORENCIA), rotate injection sites, and to avoid injections into areas where the skin is tender, bruised, red, or hard.

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

3 DOSAGE FORMS AND STRENGTHS

3.1 Intravenous Infusion

For injection: 250 mg 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)].

3.2 Subcutaneous Use

Injection: 50 mg/0.4 mL, 87.5 mg/0.7 mL, and 125 mg/mL of a clear to slightly opalescent, colorless to pale-yellow solution in a single-dose prefilled glass syringe.

Injection: 125 mg/mL of a clear to slightly opalescent, colorless to pale-yellow solution in a single-dose prefilled ClickJect autoinjector.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risk of Infection with Concomitant Use of TNF Antagonists, Other Biologic RA/Psa Therapy, or JAK Inhibitors

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. Additionally, concomitant use of ORENCIA with other biologic RA/Psa therapy or JAK inhibitors is not recommended.

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)].

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. In addition, there are clinical considerations for administering live vaccines to infants who were exposed to ORENCIA while in utero [see Use in Specific Populations (8.1)]. Based on its mechanism of action, ORENCIA may blunt the effectiveness of some immunizations.

### 5.5 Increased Risk of Adverse Reactions When Used 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.

### 5.7 Cytomegalovirus (CMV) and Epstein-Barr Virus (EBV) Reactivation in aGVHD Prophylaxis after Hematopoietic Stem Cell Transplant (HSCT)

Post-Transplant Lymphoproliferative Disorder (PTLD) occurred in patients who received ORENCIA for aGVHD prophylaxis during unrelated HSCT. Of 116 patients who received ORENCIA, 4 patients (3.4%) experienced PTLD. All the PTLD events were associated with Epstein-Barr virus (EBV) infection. Three of the four patients were EBV serology positive at baseline; one patient had negative baseline EBV serology with donor EBV serology unknown. Three of the 4 patients discontinued acyclovir prophylaxis at day 30 post-transplant. The range of time to onset of the events was 49 to 89 days post-transplant. Monitor patients for EBV reactivation in accordance with institutional practices. Provide prophylaxis for EBV infection for 6 months post-transplantation to prevent EBV-associated PTLD [see Dosage and Administration (2.4)].

Cytomegalovirus (CMV) invasive disease occurred in patients who received ORENCIA for aGVHD prophylaxis during unrelated HSCT. Of 116 patients who received ORENCIA, 7% experienced CMV invasive diseases up to day 225 post-transplant. All the patients who experienced CMV invasive disease were CMV serology positive at baseline. The median time to onset of the event was 91 days post-transplant. CMV invasive diseases predominately involved the gastrointestinal tract [see Adverse Reactions (6.1)].

Monitor patients for CMV infection/reactivation for 6 months post-transplant regardless of the results of donor and recipient pre-transplant CMV serology. Consider prophylaxis for CMV infection/reactivation [see Dosage and Administration (2.4)].

### 6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Increased Risk of Infection with Concomitant Use with TNF Antagonists, Other Biologic RA/PsA Therapy, or JAK Inhibitors [see Warnings and Precautions (5.1)]
- Hypersensitivity [see Warnings and Precautions (5.2)]
- Infections [see Warnings and Precautions (5.3)]
- Increased Risk of Adverse Reactions When Used in Patients with Chronic Obstructive Pulmonary Disease (COPD) [see Warnings and Precautions (5.5)]
- Immunosuppression [see Warnings and Precautions (5.6)]
- Cytomegalovirus (CMV) and Epstein-Barr Virus (EBV) Reactivation in aGVHD Prophylaxis after Hematopoietic Stem Cell Transplant (HSCT) [see Warnings and Precautions (5.7)]

### 6.1 Clinical Trials Experience

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.

### Adverse Reactions in Adult Patients with RA

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 (1.5)]. 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 pneumonia (0.5%), bronchitis (0.7%), and herpes zoster (0.7%). The most frequent infections resulting in discontinuation were pneumonia (0.5%), 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 3.

#### Table 3: Most Common Adverse Reactions* During Placebo-Controlled RA Studies of Intravenous ORENCIA

<table>
<thead>
<tr>
<th>Infections (n=1955)</th>
<th>Placebo (n=989)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>18%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9%</td>
</tr>
<tr>
<td>Cough</td>
<td>8%</td>
</tr>
<tr>
<td>Back pain</td>
<td>7%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>6%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>6%</td>
</tr>
<tr>
<td>Rash</td>
<td>4%</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>3%</td>
</tr>
</tbody>
</table>

* 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 influenza, 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.
ORENCIA® (abatacept)

Adverse Reactions in Patients with pJIA

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 38% [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, myalgia, and arthralgia.

A total of 6 serious adverse events [acute lymphocytic leukemia, ovarian cyst, varicella infection, disease flare (2), and joint pain] 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.

Adverse Reactions in Patients with pJIA Treated with Subcutaneous ORENCIA

Study JIA-2 was an open-label study with a 4-month short-term period and a long-term extension period that assessed the safety of subcutaneous ORENCIA in 205 pediatric patients, 2 to 17 years of age with pJIA. The adverse reaction profile in patients with pJIA treated with ORENCIA administered subcutaneously in Study JIA-2 was consistent with the adverse reaction profile in patients with pJIA treated with intravenous Study JIA-1.

There were no reported cases of hypersensitivity reactions. Local injection-site reactions occurred at a frequency of 4.4%.

Adverse Reactions in Patients Undergoing Unrelated-Donor Hematopoietic Stem Cell Transplantation (HSCT) with Intravenous ORENCIA

The data described herein were from one clinical study of ORENCIA (GVHD-1) for aGVHD prophylaxis in patients 6 years and older with hematologic malignancies who were undergoing unrelated HSCT wherein all patients were receiving calcineurin inhibitor and methotrexate as the standard of care for aGVHD prophylaxis [see Clinical Studies (14.4)].

Two cohorts were studied at 10 mg/kg (maximum dose of 1,000 mg) as an intravenous infusion over 60 minutes on the day before transplantation (Day -1), followed by administration on Days 5, 14, and 28 after transplantation:

1) A single-arm cohort of ORENCIA-treated patients (n=43) who underwent 7 of 9 Human leukocyte antigen (HLA)-matched HSCT from unrelated donors (7 of 8 cohort) and
2) A randomized cohort comprised of ORENCIA-treated patients (n=73) and placebo-treated patients (n=69) who underwent 8 of 8 HLA-matched HSCT from unrelated donors (8 of 8 cohort).

Of the 116 patients who received ORENCIA, 27 (23%) were 6 to less than 17 years of age [see Use in Specific Populations (8.4)].

The safety information from the date of first dose of ORENCIA up to Day 225 post-transplantation from this study is presented below. The incidence of adverse reactions was determined based on pooled data of ORENCIA-treated patients from the 2 study cohorts (n=116).

Serious adverse reactions reported in >5% of patients who received ORENCIA in combination with a calcineurin inhibitor and methotrexate included pyrexia (20%), pneumonia (8%), acute kidney injury (7%), diarrhea (6%), hypoglycemia (5%), and nausea (5%).

Permanent discontinuation of ORENCIA due to an adverse reaction occurred in two patients (1.7%) due to one case each of pneumonia and allergic reaction.

The most common (≥10%) adverse reactions in the ORENCIA treated patients were anemia, hypertension, CMV reactivation/CMV infection, pyrexia, pneumonia, epistaxis, CD4 lymphocytes decreased, hypermagnesemia, and acute kidney injury.

Table 4 summarizes the frequency of adverse reactions reported in the study of ORENCIA in GvHD-1.
ORENCIA® (abatacept)

6.2 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 patients with RA who were treated with intravenous ORENCIA. Thirty-four of 1993 (2%) patients who were treated 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, 9 (45%) 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.

Immunogenicity in Patients Treated for Prophylaxis of aGVHD with Intravenous ORENCIA

Immunogenicity was assessed in patients undergoing HSCT. Overall, immunogenicity incidence and associated antibody titers were low from the 4-dose intravenous ORENCIA regimen used in this study. Of the 114 immunogenicity evaluable subjects in the ORENCIA groups, none were positive during the ORENCIA treatment period (Day -1 to Day 28 following transplant). During the off-treatment period (Day 29 and up to Day 180 following transplant); 6 of 91 immunogenicity evaluable subjects (6.6%) were positive for CTLA4 and possibly Ig; 4 of the 6 positive subjects were found to have at least one positive sample with neutralizing activity. In this study, immunogenicity positive subjects only had ADA positive samples on Day 180 (off-treatment period) and thus due to the timing of the response, the impact on PK, safety, or efficacy could not be determined.

6.3 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.

7 DRUG INTERACTIONS

7.1 Immunosuppressants

Concomitant 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)].

There is insufficient experience to assess the safety and efficacy of ORENCIA administered concurrently with other biologic RA therapy, such as anakinra, or other biologic PSA therapy, and JAK inhibitors and therefore such use is not recommended. [see Warnings and Precautions (5.1)].

**Table 4: Adverse Reactions (≥10%) in Patients with aGVHD Who Received ORENCIA with a Difference Between Arms of >2% Compared to Placebo in GVHD-1**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>7 of 8 Cohort ORENCIA (N=43)</th>
<th>8 of 8 Cohort ORENCIA (N=73)</th>
<th>Placebo (N=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>56</td>
<td>56</td>
<td>69</td>
</tr>
<tr>
<td>CD4 lymphocytes decreased</td>
<td>14</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>49</td>
<td>49</td>
<td>43</td>
</tr>
<tr>
<td>General Disorders and Administrative Site Conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>28</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV Reactivation/CMV infection</td>
<td>26</td>
<td>26</td>
<td>32</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>19</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>Respiratory and Mediastinal Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>12</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>9</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>5</td>
<td>5</td>
<td>18</td>
</tr>
</tbody>
</table>

Clinically relevant adverse reactions in <10% of patients who received ORENCIA in combination with calcineurin inhibitor and methotrexate in Study GVHD-1 included EBV reactivation.
7.2 Blood Glucose Testing
Parenteral drug products containing maltose can interfere with the readings of blood glucose monitors that use test strips with glucose dehydrogenase pyruviloquinoline 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
Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ORENCIA during pregnancy. Healthcare professionals are encouraged to register patients and pregnant women are encouraged to enroll themselves by calling 1-877-311-8972.

Risk Summary
The data with ORENCIA use in pregnant women are insufficient to inform on drug-associated risk. However, there are clinical considerations for administering live vaccines to infants who were exposed to ORENCIA while in utero (see Clinical Considerations). 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.

Clinical Considerations
Infants and Administration of Live Vaccines
It is unknown if abatacept can cross the placenta into the fetus when a woman is treated with ORENCIA during pregnancy. Abatacept is an immunomodulatory agent. It is unknown if the immune response of an infant who was exposed in utero to abatacept and subsequently administered a live vaccine is impacted. Risks and benefits should be considered prior to vaccinating such infants (see Warnings and Precautions [5.4]).

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) 28 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 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.

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) 28 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 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.

8.2 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.

8.4 Pediatric Use
Polyarticular Juvenile Idiopathic Arthritis
The safety and effectiveness of ORENCIA for reducing signs and symptoms in patients 2 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis (pJIA) have been established (ORENCIA may be used as monotherapy or concomitantly with methotrexate). 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 (12.1) 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.

Subcutaneous Use: An open-label PK and safety study of subcutaneous ORENCIA in 205 pediatric patients aged 2 to 17 years old with pJIA, extrapolation of effectiveness of intravenous ORENCIA and ORENCIA in patients with pJIA and subcutaneous ORENCIA in patients with RA [see Clinical Pharmacology (12.3) and Clinical Studies (14.2)]. Given that population PK analyses (after subcutaneous ORENCIA injection) in pJIA patients showed that there was a trend toward higher clearance of abatacept with increasing body weight, subcutaneous ORENCIA dosage is weight-range based [see Dosage and Administration (2.2)].

The safety and effectiveness of ORENCIA use in pJIA in pediatric patients less than two years of age have not been established.

Acute Graft Versus Host Disease Prophylaxis
The safety and effectiveness of ORENCIA for the prophylaxis of acute graft versus host disease (aGVHD), in combination with a calcineurin inhibitor and methotrexate, in pediatric patients aged 2 years of age and older undergoing HSCT from a matched or 1-allele-mismatched unrelated donor have been established. Use of ORENCIA for this indication is supported by evidence from:

• adequate and well-controlled studies in adults and pediatric patients aged 6 years and older and administered a dose of 10 mg/kg intravenously on the day before transplantation followed by a dose of 10 mg/kg intravenously on Days 5, 14, and 28 after transplantation and

• pharmacokinetic modeling and simulations of abatacept exposure in pediatric patients aged 2 to less than 6 years administered a dose of 15 mg/kg intravenously on the day before transplantation followed by a dose of 12 mg/kg intravenously on Days 5, 14, and 28 after transplantation.

Furthermore, the course of disease is sufficiently similar in pediatric patients aged 2 years to less than 6 years to that of patients aged 6 years and older to allow extrapolation of data to younger pediatric patients [see Clinical Pharmacology (12.3) and Clinical Studies (14.4)]. No new safety signals were observed in pediatric patients aged 6 years and older in Study GVHD-1.

The safety and effectiveness of ORENCIA for this indication have not been established in pediatric patients less than 2 years of age.

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.

8.5 Geriatric Use
Rheumatoid Arthritis
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.

Acute Graft Versus Host Disease Prophylaxis
Of the 116 patients in Study GVHD-1 who received ORENCIA at a dose of 10 mg/kg for the prophylaxis of aGVHD, 12 (10%) were 65 years of age and older, and 2 (2%) patients were 75 years of age and older. Clinical studies of ORENCIA for aGVHD did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients.

10 OVERDOSAGE
ORENCIA doses up to 50 mg/kg (5 times the maximum recommended dose in patients aged 6 years and older and 3.3 times the maximum recommended dose in patients aged 2 to less than 6 years) have been administered intravenously 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.
ORENCIA® (abatacept)

11 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 kdaltons.

ORENCIA® (abatacept) for injection is a sterile, 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, 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 250 mg abatacept, maltose (500 mg), monobasic sodium phosphate (17.2 mg), and sodium chloride (14.6 mg).

ORENCIA® (abatacept) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale-yellow solution with a pH range of 6.8 to 7.4 for subcutaneous administration. ORENCIA injection is supplied as a single-dose prefilled syringe or as a single-dose ClickJect autoinjector (see Table 5).

Table 5: Contents of ORENCIA Subcutaneous Injection

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Active Ingredient Quantity and Volume</th>
<th>Inactive Ingredient Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORENCIA injection 50 mg/0.4 mL prefilled syringe</td>
<td>50 mg of abatacept in 0.4 mL of solution</td>
<td>dibasic sodium phosphate anhydrous (0.335 mg) monobasic sodium phosphate monohydrate (0.114 mg) poloxamer 188 (3.2 mg) sucrose (68 mg) qs to 0.4 mL Water for Injection, USP</td>
</tr>
<tr>
<td>ORENCIA injection 87.5 mg/0.7 mL prefilled syringe</td>
<td>87.5 mg of abatacept in 0.7 mL of solution</td>
<td>dibasic sodium phosphate anhydrous (0.587 mg) monobasic sodium phosphate monohydrate (0.200 mg) poloxamer 188 (0.6 mg) sucrose (119 mg) qs to 0.7 mL Water for Injection, USP</td>
</tr>
<tr>
<td>ORENCIA injection 125 mg prefilled syringe and ClickJect autoinjector</td>
<td>125 mg of abatacept in 1 mL of solution</td>
<td>dibasic sodium phosphate anhydrous (0.838 mg) monobasic sodium phosphate monohydrate (0.286 mg) poloxamer 188 (6 mg) sucrose (170 mg) qs to 1 mL Water for Injection, USP</td>
</tr>
</tbody>
</table>

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

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. Abatacept is a selective 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 kdaltons.

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 (MMP-3), and TNFα. The relationship of these biological response markers to the mechanisms by which ORENCIA exerts its clinical effects is unknown.

No formal pharmacodynamic analyses of biologic response markers have been performed in patients exposed to ORENCIA as prophylaxis for anVHD.

12.3 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 6).

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 TNFα 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 max and C trough at steady state observed after 85 days of treatment was 22.5 mcg/mL (6.6 to 115.8 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/hr/kg), volume of distribution (0.11 L/kg), and terminal half-life (14.3 days) were comparable between subcutaneous and intravenous administration.

Population pharmacokinetic analyses of the serum concentration data showed that clearance of abatacept increased with baseline body weight. Age and gender (when corrected for body weight) did not affect 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 (2.1)]. 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 - Subcutaneous Administration

In Study JIA-2 among patients 2 to 17 years of age, steady state of abatacept was achieved by Day 55 following the weekly body-weight–tiered subcutaneous ORENCIA dosing [see Clinical Studies (14.2)]. Comparable trough concentrations across weight tiers and age groups were achieved by the body-weight–tiered subcutaneous dosing regimen. The mean (range) trough concentration of abatacept at Day 113 was 44.4 mcg/mL (13.4 to 88.1 mcg/mL) and 46.6 mcg/mL (22.4 to 97.0 mcg/mL), and 39.5 mcg/mL (9.3 to 73.2 mcg/mL) in pediatric JIA patients weighing 10 to <25 kg, 25 to <50 kg, and ≥50 kg, respectively.

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.
ORENCIA® (abatacept) ORENCIA® (abatacept)

Adult Psoriatic Arthritis - Intra-venous 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 1,000 mg for patients weighing greater than 100 kg, or three 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 linearPK 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.

Prophylaxis of Acute Graft versus Host Disease – Intra-venous Administration

In a study of patients who received ORENCIA for prophylaxis of acute Graft Versus Host Disease (aGVHD) aged 6 years and older, the geometric mean (CV%) trough concentrations (Cmin) of abatacept on Day 63 after transplant after 4 doses utilizing weight-based dosing (10 mg/kg) the steady state of abatacept was reached by Day 57 and the geometric mean (CV%) Cmin was observed on Day 5 of the treatment period; n = 18 for the 7/8 Cohort; n = 32 for the 8/8 Cohort. Cmin, CL, Vd, and Vss are model predicted after first 10 mg/kg ORENCIA intravenous infusion.

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>7 of 8 Cohort (n=42)</th>
<th>8 of 8 Cohort (n=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum Concentration</td>
<td>59 (26-112)</td>
<td>43 (25-73)</td>
</tr>
<tr>
<td>Peak Concentration</td>
<td>221 (163-292)</td>
<td>172 (107-254)</td>
</tr>
<tr>
<td>Terminal half-life</td>
<td>20.5 (6-43)</td>
<td>20.8 (12-38)</td>
</tr>
<tr>
<td>Systemic clearance</td>
<td>0.26 (0.15-0.65)</td>
<td>0.32 (0.18-0.56)</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>0.13 (0.08-0.27)</td>
<td>0.17 (0.11-0.26)</td>
</tr>
</tbody>
</table>

In an in vitro assay, abatacept did not influence the growth of human keratinocytes at concentrations up to 100 μM. In studies of patients who received ORENCIA for prophylaxis of acute Graft Versus Host Disease (aGVHD) aged 6 years and older, the geometric mean (CV%) trough concentrations (Cmin) of abatacept on Day 63 after transplant after 4 doses utilizing weight-based dosing (10 mg/kg) the steady state of abatacept was reached by Day 57 and the geometric mean (CV%) Cmin was observed on Day 5 of the treatment period; n = 18 for the 7/8 Cohort; n = 32 for the 8/8 Cohort. Cmin, CL, Vd, and Vss are model predicted after first 10 mg/kg ORENCIA intravenous infusion.

In studies of adult mice and monkeys, inhibition of T-lymphocytes 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

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.

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 8. 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 I.

In Studies I 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 8). 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 9, 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 8. 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 8: Clinical Responses in Controlled Trials in Patients with RA

<table>
<thead>
<tr>
<th>Percent of Patients</th>
<th>Inadequate Response to DMARDs (MTX)</th>
<th>Inadequate Response to Methotrexate (MTX)</th>
<th>Inadequate Response to TNF Antagonists</th>
<th>MTX-Naive</th>
<th>Inadequate Response to MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intravenous Administration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study I</td>
<td>ORN P BO</td>
<td>ORN P BO</td>
<td>ORN P BO</td>
<td>ORN P BO</td>
<td>ORN P BO</td>
</tr>
<tr>
<td>n=32</td>
<td>n=32</td>
<td>n=32</td>
<td>n=32</td>
<td>n=32</td>
<td>n=32</td>
</tr>
<tr>
<td>ACR 20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 3</td>
<td>53%</td>
<td>31%</td>
<td>62%</td>
<td>37%</td>
<td>46%</td>
</tr>
<tr>
<td>Month 6</td>
<td>NA</td>
<td>NA</td>
<td>68%</td>
<td>40%</td>
<td>50%</td>
</tr>
<tr>
<td>Month 12</td>
<td>NA</td>
<td>NA</td>
<td>73%</td>
<td>40%</td>
<td>76%</td>
</tr>
<tr>
<td><strong>ACR 50</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 3</td>
<td>16%</td>
<td>6%</td>
<td>32%</td>
<td>8%</td>
<td>18%</td>
</tr>
<tr>
<td>Month 6</td>
<td>NA</td>
<td>NA</td>
<td>40%</td>
<td>17%</td>
<td>20%</td>
</tr>
<tr>
<td>Month 12</td>
<td>NA</td>
<td>NA</td>
<td>48%</td>
<td>18%</td>
<td>57%</td>
</tr>
<tr>
<td><strong>ACR 70</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 3</td>
<td>6%</td>
<td>0</td>
<td>13%</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>Month 6</td>
<td>NA</td>
<td>NA</td>
<td>20%</td>
<td>7%</td>
<td>10%</td>
</tr>
<tr>
<td>Month 12</td>
<td>NA</td>
<td>NA</td>
<td>29%</td>
<td>6%</td>
<td>29%</td>
</tr>
<tr>
<td><strong>Major Clinical Response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>NA</td>
<td>14%</td>
<td>2%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>DAS28-CRP &lt;2.6</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 12</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>41%</td>
</tr>
</tbody>
</table>

Table 9: Components of ACR Responses at 6 Months in Adult Patients with RA

<table>
<thead>
<tr>
<th>Study</th>
<th>Inadequate Response to MTX</th>
<th>Inadequate Response to TNF Antagonists</th>
<th>Inadequate Response to MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study III</td>
<td>ORN +MTX</td>
<td>PBO +MTX</td>
<td>ORN +DMARDs</td>
</tr>
<tr>
<td>n=424</td>
<td>n=214</td>
<td>n=256</td>
<td>n=133</td>
</tr>
<tr>
<td>Study IV</td>
<td>ORN +MTX</td>
<td>PBO +DMARDs</td>
<td></td>
</tr>
<tr>
<td>n=678</td>
<td>n=633</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study SC-1†</td>
<td>ORN SC +MTX</td>
<td>ORN N +MTX</td>
<td></td>
</tr>
<tr>
<td>n=693</td>
<td>n=678</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Component (median)</td>
<td>BL 6 M</td>
<td>BL 6 M</td>
<td>BL 6 M</td>
</tr>
<tr>
<td>Number of tender joints (0-66)</td>
<td>28 7‡</td>
<td>31 14</td>
<td>30 13‡</td>
</tr>
<tr>
<td>Number of swollen joints (0-66)</td>
<td>19 5‡</td>
<td>20 11</td>
<td>21 10‡</td>
</tr>
<tr>
<td>Pain§</td>
<td>67 27‡</td>
<td>70 50</td>
<td>73 43‡</td>
</tr>
<tr>
<td>Patient global assessment§</td>
<td>66 29‡</td>
<td>64 48</td>
<td>71 44‡</td>
</tr>
<tr>
<td>Physician global assessment§</td>
<td>69 21‡</td>
<td>68 40</td>
<td>71 32‡</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>2.2 0.9‡</td>
<td>2.1 1.8</td>
<td>3.4 1.3‡</td>
</tr>
</tbody>
</table>

† 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.

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 results of the components of the ACR response criteria for Studies III, IV, and SC-1 are shown in Table 9 (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.
14.2 Polyarticular Juvenile Idiopathic Arthritis

**Polyarticular Juvenile Idiopathic Arthritis - Intra-vascular Administration**

ORENCIA® for subcutaneous administration without an intravenous loading dose was assessed in Study JA-2, a 2-period, open-label study that included pediatric patients 2 to 17 years of age (n=205). Patients had active polyarticular disease at the time of the study and had inadequate response to at least one biologic or biologic DMARD. The JIA patient subtypes at study entry included polyarticular (79%; 20% were rheumatoid factor positive), extended and persistent oligoarticular (14%), enthesitis-related arthritis (14%), and systemic JIA (2%). ORENCIA® treatment results were similar between subcutaneous and intravenous ORENCIA® administration. The results from Study II and III are shown in Table 11. Similar results were observed in Study IV 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 11: Mean Improvement from Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) in Adult Patients with RA**

<table>
<thead>
<tr>
<th>HAQ Disability Index</th>
<th>Study II</th>
<th>Study III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ORENCIA® +MTX (n=115)</td>
<td>Placebo (n=119)</td>
</tr>
<tr>
<td>Baseline (Mean)</td>
<td>0.98a</td>
<td>0.97c</td>
</tr>
<tr>
<td>Mean Improvement</td>
<td>0.40c***</td>
<td>0.15d</td>
</tr>
</tbody>
</table>

*** 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.

- ORENCIA 3 mg/kg
- Placebo

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 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).

14.3 Adult Psoriatic Arthritis

**Psoriatic Arthritis**

The safety and efficacy of ORENCIA® with intravenous administration were assessed in Study JA-1, a three-part study including an open-label extension in pediatric patients with polyarticular juvenile idiopathic arthritis (JIA) (n=190), with moderate 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/m² 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 1,000 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 Ped 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 ≥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 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.

**Table 10: Mean Radiographic Changes in Study IIIa and Study VIb**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ORENCIA/MTX</th>
<th>Placebo/MTX</th>
<th>Differences</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSS</td>
<td>1.07</td>
<td>2.43</td>
<td>1.36</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ES</td>
<td>0.61</td>
<td>1.47</td>
<td>0.86</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>JSS score</td>
<td>0.46</td>
<td>0.97</td>
<td>0.51</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

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.
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 ACR20 response at 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 12 below.

### Table 12: Proportion of Patients With ACR Responses at Week 24 in Studies PsA-I and PsA-II

<table>
<thead>
<tr>
<th></th>
<th>PsA-I</th>
<th>PsA-II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ORENCIA Weight-Range-Based Intravenous Dosing&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>N=40</td>
<td>N=42</td>
</tr>
<tr>
<td>ACR 20</td>
<td>47.5%*</td>
<td>19.0%</td>
</tr>
<tr>
<td>ACR 50</td>
<td>25.0%</td>
<td>2.4%</td>
</tr>
<tr>
<td>ACR 70</td>
<td>12.5%</td>
<td>0%</td>
</tr>
</tbody>
</table>

<sup>*</sup>p < 0.05 versus placebo.

<sup>4</sup>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 1,000 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 ACR 20 Response<sup>a</sup> in PsA-II Study Through Week 24 (Day 169)

- **ORENCIA 125 mg (N=213)**
- **Placebo (N=211)**

<sup>a</sup>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: -2.1, 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).

### 14.4 Prophylaxis of Acute Graft versus Host Disease

#### Study GVHD-1

The efficacy of ORENCIA, in combination with a calcineurin inhibitor (CNI) and methotrexate (MTX), for the prophylaxis of acute graft versus host disease (aGVHD), was evaluated in a multicenter, two cohort clinical study (GVHD-1, NCT01743131) in patients age 6 years and older who underwent hematopoietic stem cell transplantation (HSCT) from a matched or allele-mismatched unrelated donor (URD). The two cohorts in GVHD-1 included:

1. one-open-label, single-arm study of 43 patients who underwent a 7 of 8 Human Leukocyte Antigen (HLA)-matched HSCT (7 of 8 cohort); and
2. a randomized (1:1), double-blind, placebo-controlled study of patients who underwent an 8 of 8 HLA-matched HSCT who received ORENCIA or placebo in combination with a CNI and MTX (8 of 8 cohort).

In both the 7/8 and 8/8 cohorts, ORENCIA was administered at a dose of 10 mg/kg (1,000 mg maximum dose) as an intravenous infusion over 60 minutes, beginning on the day before transplantation (Day 1), followed by administration on Days 5, 14, and 28 after transplantation. Baseline demographic and clinical characteristics of both the 7 of 8 and 8 of 8 cohorts are outlined below in Table 13.

### Table 13: Baseline Demographic and Clinical Characteristics: 7 of 8 and 8 of 8 Cohort Treated Analysis Population in Study GVHD-1

<table>
<thead>
<tr>
<th></th>
<th>7 of 8 Cohort</th>
<th>8 of 8 Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ORENCIA (+CNI and MTX) N=43</td>
<td>ORENCIA (+CNI and MTX) N=73</td>
</tr>
<tr>
<td>Age - Median</td>
<td>38</td>
<td>44</td>
</tr>
<tr>
<td>Age - Range</td>
<td>6-76</td>
<td>6-71</td>
</tr>
<tr>
<td>Gender - Male</td>
<td>27 (63)</td>
<td>41 (56)</td>
</tr>
<tr>
<td>White</td>
<td>31 (72)</td>
<td>63 (86)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>7 (16)</td>
<td>3 (4.1)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (4.7)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>7 (16)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Malignancy type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Myeloid Leukemia (AML)</td>
<td>15 (35)</td>
<td>30 (41)</td>
</tr>
<tr>
<td>Myelodysplastic Syndrome (MDS)</td>
<td>11 (26)</td>
<td>15 (21)</td>
</tr>
<tr>
<td>Acute Lymphoblastic Leukemia (ALL)</td>
<td>8 (19)</td>
<td>20 (27)</td>
</tr>
<tr>
<td>Acute leukemia or ambiguous lineage</td>
<td>1 (2.3)</td>
<td>0</td>
</tr>
<tr>
<td>Hodgkin and Non-Hodgkin lymphoma</td>
<td>1 (2.3)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Acute Lymphoblastic Lymphoma in 2nd or Greater Complete Remission</td>
<td>1 (2.3)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Chronic Myelomonocytic leukemia</td>
<td>1 (2.3)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Chronic Myelogenous leukemia</td>
<td>4 (9)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Not reported</td>
<td>1 (2.3)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>GVHD Prophylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>16 (37)</td>
<td>11 (15)</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>27 (63)</td>
<td>62 (85)</td>
</tr>
<tr>
<td>Type of Graft</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone Marrow</td>
<td>21 (49)</td>
<td>33 (45)</td>
</tr>
<tr>
<td>Cytokine Mobilized Peripheral Blood (PSSC)</td>
<td>22 (51)</td>
<td>40 (55)</td>
</tr>
<tr>
<td>Conditioning Regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBI and Chemotherapy</td>
<td>11 (26)</td>
<td>20 (27)</td>
</tr>
<tr>
<td>Busulfan and Cyclophosphamide</td>
<td>13 (30)</td>
<td>28 (38)</td>
</tr>
<tr>
<td>Busulfan and Fludarabine</td>
<td>8 (19)</td>
<td>7 (10)</td>
</tr>
<tr>
<td>Melphalan and Fludarabine</td>
<td>11 (26)</td>
<td>18 (25)</td>
</tr>
</tbody>
</table>

Efficacy was established based on overall survival (OS) and grade II-IV aGVHD free survival (GFS) results assessed at Day 180 post-transplantation. ORENCIA + CNI and MTX did not significantly improve grade III-IV GFS versus placebo + CNI and MTX at Day 180 post-transplantation. The efficacy results of the GVHD-1 8 of 8 cohort are shown in Table 14.
ORENCA® (abatacept)

ORENCA® (abatacept) injection and ORENCA® ClickJect (abatacept) injection are clear for Subcutaneous Use vial (one may use less than the full contents of the vial or use more than one vial) with a after reconstitution and dilution. It is supplied as an individually packaged, single-dose syringe provides ORENCIA in the following packages:

- NDC 0003-2187-10: in a clamshell presentation
- NDC 0003-2187-13: in a carton presentation

For Intravenous Infusion
ORENCA® (abatacept) for injection is a 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:

- NDC 0003-2187-10: in a clamshell presentation
- NDC 0003-2187-13: in a carton presentation

For Subcutaneous Use
ORENCA® (abatacept) injection and ORENCA® ClickJect (abatacept) injection are clear to slightly opalescent, colorless to pale yellow solutions for subcutaneous administration.

Prefilled Syringe
ORENCA (abatacept) injection, 50 mg/0.4 mL, 87.5 mg/0.7 mL, and 125 mg/mL, is supplied as single-dose disposable prefilled glass syringes 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 packages:

- NDC 0003-2814-11 (50 mg/0.4 mL): pack of 4 syringes with a passive needle safety guard
- NDC 0003-2818-11 (87.5 mg/0.7 mL): pack of 4 syringes with a passive needle safety guard
- NDC 0003-2818-11 (125 mg/mL): pack of 4 syringes with a passive needle safety guard

Table 14: Efficacy Results in 8 of 8 Cohort in Study GVHD-1 at Day 180 Post-Transplantation

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>ORENCIA (+CNI and MTX)</th>
<th>Placebo (+CNI and MTX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=73</td>
<td>87% (77%, 93%)</td>
<td>75% (63%, 84%)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.55 (0.26, 1.18)</td>
<td></td>
</tr>
<tr>
<td>n=72</td>
<td>50% (38%, 61%)</td>
<td>32% (21%, 43%)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.54 (0.35, 0.83)</td>
<td></td>
</tr>
<tr>
<td>Overall Survival Rate (95% CI)</td>
<td>97% (89%, 99%)</td>
<td>84% (73%, 91%)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.33 (0.12, 0.93)</td>
<td></td>
</tr>
</tbody>
</table>

In an exploratory analysis of the 7 of 8 cohort of ORENCIA-treated patients (n=43), the rates of Grade III-IV GVHD-free survival, Grade II-IV GVHD-free survival, and overall survival at day 180 post-transplantation were 95% (95% CI 89%, 99%), 53% (95% CI 38%, 67%), and 98% (95% CI 85%, 100%), respectively.

Study GVHD-2
GVHD-2 was a clinical study that used data from the Center for International Blood and Marrow Transplant Research (CIBMTR). The study analyzed outcomes of ORENCIA in combination with a CNI and MTX, versus a CNI and MTX alone, for the prophylaxis of aGVHD, in patients 6 years of age or older who underwent HSCT from a 1 allele-mismatched UDR between 2011 and 2018. The ORENCIA + CNI and MTX-treated group (n=54) included 42 patients from GVHD-1, in addition to 12 patients treated with ORENCIA outside of GVHD-1. The comparator group (n=162) was randomly selected in a 3:1 ratio to the ORENCIA-treated group from the CIBMTR registry from patients who had not received ORENCIA during the study period. Analyses used propensity score matching and inverse probability of treatment weighting to help address the impact of selection bias.

Efficacy was based on Overall Survival (OS) at Day 180 post-transplantation. The OS rate at Day 180 in the ORENCIA in combination with CNI and MTX group was 98% (95% CI 78, 100) and the OS rate at Day 180 in the CNI and MTX group was 75% (95% CI 67, 82).

16 HOW SUPPLIED/STORAGE AND HANDLING

For Intravenous Infusion
ORENCA® (abatacept) ClickJect, 125 mg/mL, is supplied as a single-dose disposable prefilled autoinjector. The Type I glass syringe contained in the autoinjector has a coated stopper and fixed stainless steel needle (5 bevel, 29-gauge special thin wall, ½-inch needle) covered with a rigid needle shield. The autoinjector provides 125 mg of abatacept in 1 mL, and is provided in the following package:

- NDC 0003-2188-51: pack of 4 autoinjectors

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Increased Risk of Infection with Concomitant Use With Immunosuppressants for RA
Inform patients that the concomitant use with other immunosuppressives (e.g., biologic DMARDs, JAK inhibitors) is not recommended [see Warnings and Precautions (5.1) and Drug Interactions (7.1)].

Hypersensitivity
Inform patients to immediately tell their healthcare professional if they experience symptoms of an allergic reaction on the day of administration or the day after ORENCIA administration [see Warnings and Precautions (5.2)].

Infections
Inform patients that serious infections have been reported in patients receiving ORENCIA [see Warnings and Precautions (5.3)].

Immunizations
Inform patients that live vaccines should not be given concurrently with ORENCIA or within 3 months of its discontinuation [see Warnings and Precautions (5.4)].

Pregnancy
Inform patients that there is a Pregnancy Exposure Registry [see Use in Specific Populations (8.1)].

Blood Glucose Testing
Maltose is contained in ORENCIA for intravenous administration and can give falsely elevated blood glucose readings with certain blood glucose monitors on the day of ORENCIA infusion. Advise patients treated with intravenous ORENCIA who are using GDH-PQQ-based monitoring systems for glucose (e.g., diabetics) to consider using other methods for glucose monitoring. This recommendation is not applicable to patients treated with subcutaneous ORENCIA [see Drug Interactions (7.2)].

Disposal of Prefilled Syringes and ClickJect Autoinjectors
Advise patients to follow disposal instructions in the Instructions for Use. A puncture-resistant container for disposal of needles and syringes should be used. Instruct patients that they will need to follow their community guidelines for the correct way to dispose of their sharps disposal container. Instruct patients not to recycle their used sharps disposal container.

Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA
U.S. License Number 1713
PATIENT INFORMATION
ORENCIA® (oh-REN-see-ah)
(abatacept)
for injection, for intravenous use
ORENCIA® (oh-REN-see-ah)
(abatacept)
injection, for subcutaneous use

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. In adults, ORENCIA may be used alone or with other RA treatments other than tumor necrosis factor (TNF) antagonists.

● people 2 years of age and older with moderate to severe polyarticular juvenile idiopathic arthritis (pJIA). ORENCIA may be used alone or with methotrexate.

● adults with active psoriatic arthritis (PsA). In adults, ORENCIA can be used alone or with other PsA treatments.

ORENCIA is also used for the preventative treatment of acute graft versus host disease (aGVHD), in combination with a calcineurin inhibitor and methotrexate, in:

● people 2 years of age and older undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated-donor.

It is not known if ORENCIA is safe and effective in children less than two years of age for the treatment of pJIA.

It is not known if ORENCIA is safe and effective in children less than two years of age for the preventative treatment of aGVHD.

Before you receive or use ORENCIA, tell your healthcare provider about all of 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 during treatment with ORENCIA, you may have a higher chance for getting serious side effects.

● have an infection that will not go away or an infection that keeps coming back.

● are allergic to abatacept or any of the ingredients in ORENCIA. See the end of this Patient Information leaflet for a complete list of ingredients in ORENCIA.

● have or have had inflammation of your liver due to an infection (viral hepatitis). Your healthcare provider may examine you for hepatitis before treatment with ORENCIA.

● have had a lung infection called tuberculosis (TB), a positive skin test for TB, or you recently have been in close contact with someone who has had TB. Your healthcare provider may examine you for TB or perform a skin test before treatment with ORENCIA. Symptoms of TB may include:
  ○ a cough that does not go away
  ○ fever
  ○ weight loss
  ○ night sweats

● have a history of Epstein-Barr Virus (EBV) or Cytomegalovirus (CMV) in people receiving ORENCIA for preventative treatment of aGVHD during HSCT from an unrelated donor.

● are scheduled to have surgery.

● recently received a vaccination or are scheduled for a vaccination.

● have a history of a breathing problem called chronic obstructive pulmonary disease (COPD).

● have diabetes and use a blood glucose monitor to check your blood sugar (blood glucose) levels. ORENCIA for intravenous infusion (given through a needle placed in a vein) 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 healthcare provider may tell you to use a different way to monitor your blood sugar levels.

● ORENCIA for subcutaneous injection (injected under the skin) does not contain maltose. You do not need to change your blood sugar monitoring if you are using ORENCIA subcutaneously.

● are pregnant or plan to become pregnant. It is not known if ORENCIA can harm your unborn baby. If you took ORENCIA during pregnancy, talk to your healthcare provider before your baby receives any vaccines.

● There is 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. Women are encouraged to call the registry themselves or ask their healthcare provider to contact the registry for them by calling 1-877-311-8972.
ORENcia® (abatacept)

- are breastfeeding or plan to breastfeed. It is not known if ORENCIA passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you use ORENCIA.
- Some people treated with ORENCIA have developed skin cancer. Tell your healthcare provider if you have a family or personal history of skin cancer, and if you see any growths or changes in the appearance of your skin during or after your treatment with ORENCIA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

ORENCIA may affect the way other medicines work, and other medicines may affect the way ORENCIA works causing serious side effects.

Especially tell your healthcare provider if you take other biologic medicines that may affect your immune system, such as:
- Enbrel® (etanercept)
- Humira® (adalimumab)
- Remicade® (infliximab)
- Kineret® (anakinra)
- Rituxan® (rituximab)
- Simponi® (golimumab)
- Cimzia® (certolizumab pegol)
- Actemra® (tocilizumab)

You may have a higher chance of getting a serious infection if you take ORENCIA with other biologic medicines that may affect your immune system.

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

How will I receive or use ORENCIA?

For treatment of RA, pJIA or PsA:
- You may receive ORENCIA given by a healthcare provider through a vein in your arm (intravenous infusion). It takes about 30 minutes to give you the full dose of medicine. You will then receive ORENCIA 2 weeks and 4 weeks after the first dose and then every 4 weeks.
- You may also receive ORENCIA as an injection under your skin (subcutaneous). For home use, ORENCIA comes in a prefilled syringe or prefilled ClickJect autoinjector. Your healthcare provider will prescribe the type that is best for you. If your healthcare provider decides that you or a caregiver can give your injections of ORENCIA prefilled syringes or ORENCIA ClickJect autoinjectors at home, you or your caregiver should receive training on the right way to prepare and inject ORENCIA. Do not try to inject ORENCIA until you have been shown the right way to give the injections by your healthcare provider.
- Your healthcare provider will tell you how much ORENCIA to use and when to use it.

See the Instructions for Use at the end of this Patient Information leaflet for instructions about the right way to prepare and give your ORENCIA injections at home.

For preventative treatment of aGVHD:
- You will receive ORENCIA by a healthcare provider through a vein in your arm (intravenous infusion) over 60 minutes on the day before transplantation (Day -1). You will then receive ORENCIA on Days 5, 14, and 28 after transplantation.
- Your healthcare provider may give you antiviral medicines before, during, and after your transplantation to help prevent Epstein-Barr Virus (EBV) and Cytomegalovirus (CMV) infections.

What are the possible side effects of ORENCIA?

ORENcia can cause serious side effects including:
- infections. ORENCIA can make you more likely to get infections or make the infection that you have get worse. Some people have died from these infections. Call your healthcare provider right away if you have any symptoms of an infection. Symptoms of an infection may include:
  - fever
  - feel very tired
  - have a cough
  - have flu-like symptoms
  - warm, red, or painful skin
- allergic reactions. Allergic reactions can happen to people who are treated with ORENCIA. Call your healthcare provider or go to the emergency room right away if you have any symptoms of an allergic reaction. Symptoms of an allergic reaction may include:
  - hives
  - swollen face, eyelids, lips, or tongue
  - trouble breathing
- hepatitis B infection in people who carry the virus in their blood. If you are a carrier of the hepatitis B virus (a virus that affects the liver), the virus can become active during treatment with ORENCIA. Your healthcare provider may do a blood test before you start treatment with ORENCIA.
vaccinations. You should not receive ORENCIA with certain types of vaccines (live vaccines). You can receive non-live vaccines, such as pneumococcal and inactivated influenza (flu) vaccines. ORENCIA may also cause some vaccinations to be less effective. Talk with your healthcare provider about your vaccination plans.

breathing problems in people with Chronic Obstructive Pulmonary Disease (COPD). You may get certain respiratory problems more often if you receive ORENCIA and have COPD. Symptoms of respiratory problems include:
- COPD that becomes worse
- trouble breathing
- cough

cancer (malignancies). Certain kinds of cancer have been reported in people using ORENCIA. It is not known if ORENCIA increases your chance of getting certain kinds of cancer.

Cytomegalovirus (CMV) and Epstein-Barr Virus (EBV) infections. CMV and EBV infections and return of CMV and EBV (reactivation) have happened in people receiving ORENCIA for preventative treatment of aGVHD during unrelated HSCT. Your healthcare provider will monitor you for 6 months after transplantation and may treat you with medicines to help prevent CMV and EBV infection if needed.

The most common side effects of ORENCIA in people with RA include:
- headache
- sore throat
- nausea
- upper respiratory tract infection
- diarrhea
- fever
- abdominal pain
- cough
- nausea

In children and adolescents, other side effects may include:
- diarrhea
- fever
- abdominal pain
- cough
- abdominal pain

The most common side effects of ORENCIA in prevention of aGVHD include:
- low red blood cell count
- nosebleed
- high blood pressure
- decreased CD4 lymphocytes
- CMV infection
- increased levels of magnesium in the blood
- fever
- kidney problems
- pneumonia
- pneumonia

These are not all of the possible side effects of ORENCIA.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ORENCIA?
- Store ORENCIA in the refrigerator at 36°F to 46°F (2°C to 8°C).
- Keep ORENCIA in the original package and out of the light.
- Do not freeze ORENCIA.
- Safely throw away medicine that is out of date or no longer needed.

Keep ORENCIA and all medicines out of the reach of children.

General information about the safe and effective use of ORENCIA
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ORENCIA for a condition for which it was not prescribed. Do not give ORENCIA to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about ORENCIA that is written for health professionals.

What are the ingredients in ORENCIA?
Active ingredient: abatacept
Intravenous inactive ingredients: maltose, monobasic sodium phosphate, sodium chloride for administration
Subcutaneous inactive ingredients: sucrose, poloxamer 188, monobasic sodium phosphate monohydrate, dibasic sodium phosphate anhydrous, water for injection

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For more information, go to www.ORENCIA.com or call 1-800-ORENCIA.
ORENCIA® (abatacept)

INSTRUCTIONS FOR USE
ORENCIA® (oh-REN-see-ah)
(abatacept)
Prefilled Syringe with BD UltraSafe Passive™ Needle Guard

ORENCIA® Prefilled Syringe with BD UltraSafe Passive™ Needle Guard
(abatacept) Injection

Read these instructions before you start using your ORENCIA Prefilled Syringe and each time you get a refill. There may be new information. Before you use the prefilled syringe for the first time, make sure your healthcare provider shows you the right way to use it and decides that you or a caregiver may be able to give your injections of ORENCIA at home.

Important:
● Keep the Prefilled Syringe in the refrigerator until ready to use.
● Do not freeze.

Before You Begin: Get to Know Your Prefilled Syringe

There are 3 types of prefilled syringes:

- **50 mg/0.4 mL:** white plunger
- **87.5 mg/0.7 mL:** light blue plunger
- **125 mg/mL:** orange plunger

Continued on Next Page
The type of prefilled syringe you receive depends on the dose prescribed by your healthcare provider. The 125 mg/mL prefilled syringe is shown below.

Before Use

The prefilled syringe has a **flange extender** that makes it easier to hold and inject, and a **needle guard** that automatically covers the needle after a complete injection.

- **DO NOT** remove the needle cover until you are ready to inject.
- **DO NOT PULL** back on the plunger at any time.
- **DO NOT RECAP** the prefilled syringe at any time, as this may damage, bend, or break the needle.

Go to Step 1
ORENClA® (abatacept)

Step 1: Preparing for an ORENClA Injection

Gather and place supplies for your injection on a clean, flat surface.

Only the prefilled syringe is included in the package:

- Alcohol swab
- Prefilled Syringe with UltraSafe Passive Needle Guard
- Adhesive bandage
- Sharps disposal container
- Cotton ball or gauze

Let your Prefilled Syringe warm up.

Remove one prefilled syringe from the refrigerator and wait 30 minutes to allow it to reach room temperature.

- Do not speed up the warming process in any way, such as using the microwave or placing the syringe in warm water.
- Do not remove the needle cover while allowing the prefilled syringe to reach room temperature.

Wash your hands well with soap and water.
ORENCIA® (abatacept)

Step 2: Examine the Prefilled Syringe

Hold the prefilled syringe by the body with the needle cover pointing down as shown.

- **Check the expiration date** printed on the label. **Do not** use if the expiration date has passed.

- **Check the prefilled syringe for damage.** **Do not** use if it is cracked or broken.

Check the Liquid.

- **Check the liquid** in the prefilled syringe through the viewing window. It should be clear and colorless to pale yellow.

**Do not inject** if the liquid is cloudy, discolored, or has particles in it.

*Note: the 50 mg prefilled syringe is shown.

**Note:** It is normal to see an air bubble. **Do not** attempt to remove it.

Go to Step 3
Step 3: Check the Dose on the Prefilled Syringe

Hold the syringe at eye level. Look closely to make sure that the amount of liquid in the prefilled syringe is **at or just above the fill line** for your prescribed dose:

*Do not* use if your prefilled syringe does not have the correct amount of liquid. Call your pharmacist immediately.

Go to Step 4
Step 4: Choose and Prepare an Injection Site

Choose your injection site.

Choose your injection site in either the stomach (abdomen), front of the thighs, or outer area of upper arm (only if caregiver administered).

Rotate injection site.

- Each week you can use the same area of your body, but use a different injection site in that area.
- Do not inject into an area where the skin is tender, bruised, red, scaly, or hard. Do not give the injection in any areas with scars or stretch marks.
- Record the date, time, and site where you inject.

Gently clean injection site.

- Wipe the injection site with an alcohol swab and let it air dry.
- Do not touch the injection site again before giving the injection.
- Do not fan or blow on the clean area.

Remove the needle cover by holding the body of the prefilled syringe with one hand and pulling the cover straight off with your other hand.

Do not put the needle cover back on the needle after you remove it. Throw away the needle cover in your household trash.

- Do not use the prefilled syringe if it is dropped after the needle cover is removed.
- Do not use the prefilled syringe if the needle is damaged or bent.

Note: It is normal to see a drop of fluid leaving the needle.

DO NOT RECAP the Prefilled Syringe, as this may damage the needle.

Go to Step 5
Step 5: Inject Your Dose of ORENCIA

Hold the body of the prefilled syringe in your hand using your thumb and index finger. With your other hand, pinch the area of skin you cleaned.

Insert the needle.

Gently insert the needle into the pinched skin at a 45° angle.

Complete all steps to deliver your full dose of the medicine.

Inject: push the plunger with your thumb as far as it will go.

Release Needle Guard: slowly lift your thumb from the plunger to activate the needle guard.

Confirm: after a complete injection, the needle guard will cover the needle and you may hear a click.

Remove the prefilled syringe and let go of the pinched skin.

Go to Step 6
Step 6: After the Injection

Care of injection site:

- There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site.
- Do not rub the injection site.
- If needed, you may cover the injection site with an adhesive bandage.

Disposing of used Prefilled Syringes:

- Put your used ORENCIA prefilled syringes in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and prefilled syringes in your household trash.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA’s website at: http://www.fda.gov/safesharpsdisposal.
- Do not throw away (dispose of) your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.
ORENCIA® (abatacept)

See Frequently Asked Questions for additional disposal information.

If your injection is administered by a caregiver, this person must also be careful handling the syringe to prevent accidental needle stick injury and possibly spreading infection.

Keep ORENCIA prefilled syringes and the disposal container out of the reach of children.

How to store ORENCIA Prefilled Syringe

- Store ORENCIA in the refrigerator at 36°F to 46°F (2°C to 8°C).
- Keep ORENCIA in the original package and out of the light.
- Do not freeze ORENCIA.
- Safely throw away medicine that is out of date or no longer needed.

Frequently Asked Questions

Q. Why do I need to allow the prefilled syringe to warm up at room temperature for 30 minutes prior to injecting?
A. This step is primarily for your comfort. Never try to speed up the warming process in any way, like using the microwave or placing the syringe in warm water.

Q. Is it necessary to hold the skin pinch during the entire time I inject the dose?
A. You must pinch the skin during needle insertion however, for your comfort you may release the skin pinch as you deliver the injection.

Q. What if my prefilled syringe appears to be broken or damaged?
A. Do not use the prefilled syringe. Contact your healthcare provider or pharmacist for further instructions.

Q. What if I cannot clearly see the liquid inside the syringe?
A. Look at the syringe closely by holding at eye level and up to the light. You may tilt the syringe slowly to get a better view of the drug fluid. If you still have trouble, contact your healthcare provider or pharmacist for further instructions.

Q. Is it normal to feel a little bit of burning or pain during injection?
A. You may feel a prick from the needle. Sometimes, the medicine can cause slight irritation near the injection site. Discomfort should be mild to moderate. If you have any side effects, including pain, swelling, or discoloration near the injection site, contact your healthcare provider.

Q. How should I dispose of a used prefilled syringe?
A. Place the used prefilled syringe into an FDA-cleared sharps disposal container. If you do not have one you may use a household container that is:
- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use, leak-resistant, and properly labeled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and injector pens. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.

Continued on Next Page
Frequently Asked Questions (Continued)

Q. **How should I keep my prefilled syringes cool while traveling?**
A. Store them in a cool carrier between 36°F to 46°F (2°C to 8°C). Do not freeze them. Keep them in the original carton and protected from light. Your healthcare provider may know about special carrying cases.

Q. **Can I take my prefilled syringes on an airplane?**
A. Generally you are allowed to carry your prefilled syringes with you on an airplane. Do not put them in your checked luggage. You should carry your prefilled syringes with you in your travel cooler at a temperature of 36°F to 46°F (2°C to 8°C). Keep your prefilled syringes in the original carton, and with its original preprinted labels and protected from light.

Q. **What if my prefilled syringe does not stay cool for an extended period of time? Is it dangerous to use?**
A. Contact 1-800-673-6242 for more information.

If you have questions or concerns about your prefilled syringe, please contact your healthcare provider or call our toll-free help line at 1-800-673-6242.
Before You Begin

Get to know the ClickJect Autoinjector

- The Autoinjector automatically delivers the medicine. The transparent tip locks over the needle once the injection is complete and the Autoinjector is removed from the skin.
- Do not remove the orange needle cover until you are ready to inject.

Before Use

Gather supplies for your injection on a clean, flat surface (only the ClickJect Autoinjector is included in the package):

- Alcohol swab
- Adhesive bandage
- Cotton ball or gauze
- ClickJect Autoinjector
- Sharps disposal container

After Use

Go to Step 1
Step 1: Prepare Your Autoinjector

Let your ClickJect Autoinjector warm up.

Remove one Autoinjector from the refrigerator and let it rest at room temperature for **30 minutes**.

**Do not** remove the Autoinjector needle cover while allowing it to reach room temperature.

Wash your hands well with soap and water.

Examine the ClickJect Autoinjector:

- **Check expiration date** printed on the label. **Do not** use if past the expiration date.
- **Check the Autoinjector for damage. Do not** use if it is cracked or broken.
- **Check the liquid** through the viewing window. It should be clear and colorless to pale yellow. You may see a small air bubble. You do not need to remove it. **Do not inject** if the liquid is cloudy, discolored, or has particles in it.

Step 2: Prepare for Injection

Choose your injection site in either the stomach (abdomen), front of the thighs, or outer area of upper arm (only if caregiver administered).

Rotate injection site.

- Each week you can use the same area of your body, but use a different injection site in that area.
- **Do not** inject into an area where the skin is tender, bruised, red, scaly, or hard. **Do not** give the injection in any areas with scars or stretch marks.
- Record the date, time, and site where you inject.

Gently clean injection site:

- Wipe the injection site with an alcohol swab and let it air dry.
- **Do not** touch the injection site again before giving the injection.
- **Do not** fan or blow on the clean area.

Pull orange needle cover STRAIGHT off.

- **DO NOT RECAP** the Autoinjector.
- Throw away (discard) the needle cover in your household trash.
- **Do not** use the Autoinjector if it is dropped after the needle cover is removed.

Note: It is normal to see a drop of fluid leaving the needle.
Step 3: Inject Your Dose

**Position the Autoinjector** so you can see the **viewing window** and it is at a 90° angle to the injection site. With your other hand, gently **pinch the cleaned skin**.

Complete all steps to deliver your full dose of medicine:

- **Push DOWN** on the skin to unlock the Autoinjector.
- **Press button, HOLD for 15 seconds AND watch window.**
  - You will hear a click as the injection begins.
  - To deliver the full dose of medicine, hold the Autoinjector in place for 15 seconds **AND** wait until the blue indicator stops moving in window.

- **Remove the ClickJect Autoinjector** from the injection site by lifting it straight up. After you remove it from your skin, the transparent tip will lock over the needle. Release skin pinch.

Go to Step 4

Step 4: After the Injection

**Care of injection site:**

- There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site.
- **Do not** rub the injection site.
- If needed, you may cover the injection site with an adhesive bandage.
Disposing of used ClickJect Autoinjectors:

- Put your used ClickJect Autoinjector in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and prefilled syringes in your household trash.

- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak resistant, and
  - properly labeled to warn of hazardous waste inside the container.

- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA’s website at: http://www.fda.gov/safesharpsdisposal.

- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

See Frequently Asked Questions for additional disposal information.

If your injection is administered by a caregiver, this person must also handle the Autoinjector carefully to prevent accidental needle stick injury and possibly spreading infection.

Keep Autoinjector and the disposal container out of the reach of children.

How to store ORENCIA ClickJect Autoinjector

- Store ORENCIA in the refrigerator at 36°F to 46°F (2°C to 8°C).
- Keep ORENCIA in the original package and out of the light.
- Do not freeze ORENCIA.
- Safely throw away medicine that is out of date or no longer needed.
Frequently Asked Questions

Q. Why do I need to allow the Autoinjector to warm up at room temperature for 30 minutes prior to injecting?
A. This step is primarily for your comfort. If the medicine is cold, the injection may take longer than 15 seconds. Never try to speed the warming process in any way, like using the microwave or placing the Autoinjector in warm water.

Q. What if I accidentally remove the needle cover (orange cap) before I’m ready to use the Autoinjector?
A. If you remove the cover before you are ready to use the Autoinjector, be careful. Do not try to replace it. Use the Autoinjector as soon as possible. While you prepare for the injection, carefully place the Autoinjector on its side on a clean, flat surface. Be sure to keep the Autoinjector away from children.

Q. What if the Autoinjector appears to be broken or damaged?
A. Do not use the Autoinjector. Contact your healthcare provider or pharmacist for further instructions.

Q. What if the injection was not triggered?
A. Before the injection can be triggered, the device must be unlocked. To unlock, firmly push the Autoinjector down on the skin without touching the button. Once the stop-point is felt, the device is unlocked and can be triggered by pushing the button.

Q. I feel a little bit of burning or pain during injection. Is this normal?
A. When giving an injection, you may feel a prick from the needle. Sometimes, the medicine can cause slight irritation near the injection site. If this occurs, the discomfort should be mild to moderate. If you experience any side effects, including pain, swelling, or discoloration near the injection site, contact your healthcare provider or pharmacist immediately. You are encouraged to report side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Q. How do I know I received my full dose?
A. Before lifting the Autoinjector from the injection site, check to ensure that the blue indicator has stopped moving. Then, before disposing of the Autoinjector, check the bottom of the transparent viewing window to make sure there is no liquid left inside. If the medicine has not been completely injected, consult your healthcare provider or pharmacist.

Q. How should I dispose of a used Autoinjector?
A. Place used Autoinjector into an FDA-cleared sharps disposal container right away after use.
   - If you do not have one, you may use a household container that is:
     - made of a heavy-duty plastic,
     - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
     - upright and stable during use, leak-resistant, and properly labeled to warn of hazardous waste inside the container.
   - When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and Autoinjectors. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA’s website at: http://www.fda.gov/safesharpsdisposal.
   - Do not recycle your used sharps disposal container.

Continued on Next Page
Q. How should I keep my Autoinjector cool while traveling?

A. Your healthcare provider or pharmacist may be familiar with special carrying cases for injectable medicines. Store at 36°F to 46°F (2°C to 8°C). Do not freeze. Protect from light.

Q. Can I take my Autoinjector on board an aircraft?

A. Generally, this is allowed. Be sure to pack your Autoinjector in your carry-on, and do not put it in your checked luggage. You should carry it with you in your travel cooler at a temperature of 36°F to 46°F (2°C to 8°C) until you are ready to use it. Airport security procedures and airline policies change from time to time, so it’s best to check with airport authorities and the airline for any special rules. Prior to flying, get a letter from your healthcare provider to explain that you are traveling with prescription medicine that uses a device with a needle; if you are carrying a sharps container in your carry-on baggage, notify the screener at the airport.

Q. What if my Autoinjector does not stay cool for an extended period of time? Is it dangerous to use?

A. Contact 1-800-673-6242 for details.

If you have questions or concerns about your Autoinjector, please contact a healthcare provider or call our toll-free help line at 1-800-673-6242.

Bristol-Myers Squibb Company
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This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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Revised March 2017