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.

Preparation and Administration Instructions
- Administer as a 30-minute intravenous infusion (2.4)
- See the Full Prescribing Information for preparation and administration instructions for intravenous infusion and recommendations for subcutaneous use (2.4, 2.5). Prepare ORENCIA (abatacept) using only the silicone-free disposable syringe (2.4)

Intravenous Infusion
- For injection: 250 mg lyophilized powder in a single-dose vial (may use less than full contents of vial or use more than one vial) (3)

Subcutaneous Use
- Injection: 50 mg/0.4 mL, 87.5 mg/0.7 mL, 125 mg/mL solution in single-dose prefilled syringes (3)
- Injection: 125 mg/mL solution in a single-dose prefilled ClickJect™ autoinjectors (3)

CONTRAINDICATIONS
None (4)
2.1 Dosage in Adult Rheumatoid Arthritis

For adult patients with RA, administer as an intravenous infusion or as a subcutaneous dose is used, administer the first subcutaneous injection within one day of the infusion.

Subcutaneous Dosing Regimen

Administer ORENCIA in prefilled syringes or in ORENCIA ClickJect™ autoinjector by subcutaneous injection once weekly [see Dosage and Administration (2.5)].

4. 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 needle of the vial to reconstitute using the ORENCIA vial.

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.

Table 2: Dose of ORENCIA (abatacept) for Subcutaneous Administration in Patients 2 Years of Age or Older with JIA

<table>
<thead>
<tr>
<th>Body Weight of Pediatric Patient</th>
<th>Dose (once weekly)</th>
</tr>
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<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 determines it is appropriate. The ability of pediatric patients to self-inject with the autoinjector has not been tested.

2.3 Dosage in Adult Psoriatic Arthritis

For adult patients with psoriatic arthritis, administer as an intravenous infusion or a subcutaneous injection. 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 specified in Table 1. Following the initial intravenous administration, administer an intravenous infusion at 2 and 4 weeks and every 4 weeks thereafter.

Subcutaneous Dosing Regimen

Administer 125 mg of ORENCIA subcutaneously once weekly (no intravenous loading dose is needed) [see Dosage and Administration (2.5)]. For patients switching from ORENCIA intravenous infusions to subcutaneous administration, administer the first subcutaneous dose instead of the next scheduled intravenous dose.

14 CLINICAL STUDIES

14.1 Adult Rheumatoid Arthritis

ORENCIA is indicated for the treatment of moderate to severely active polyarticular juvenile idiopathic arthritis.

Body Weight of Pediatric Patient Dose (once weekly)

| Body Weight of Pediatric Patient Dose (once weekly) |
|----------------------------------|--------------------|
| 10 to less than 25 kg            | 50 mg              |
| 25 to less than 50 kg            | 87.5 mg            |
| 50 kg or more                    | 125 mg             |

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 determines it is appropriate. The ability of pediatric patients to self-inject with the autoinjector has not been tested.

2.3 Dosage in Adult Psoriatic Arthritis

For adult patients with psoriatic arthritis, administer as an intravenous infusion or a subcutaneous injection. 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 specified in Table 1. Following the initial intravenous administration, administer an intravenous infusion at 2 and 4 weeks and every 4 weeks thereafter.

Subcutaneous Dosing Regimen

Administer 125 mg of ORENCIA subcutaneously once weekly (no intravenous loading dose is needed) [see Dosage and Administration (2.5)]. For patients switching from ORENCIA intravenous infusions to subcutaneous administration, administer the first subcutaneous dose instead of the next scheduled intravenous dose.

2.4 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 needle of the vial to reconstitute using the ORENCIA vial.

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.

Table 2: Dose of ORENCIA (abatacept) for Subcutaneous Administration in Patients 2 Years of Age or Older with JIA

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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 determines it is appropriate. The ability of pediatric patients to self-inject with the autoinjector has not been tested.

2.3 Dosage in Adult Psoriatic Arthritis

For adult patients with psoriatic arthritis, administer as an intravenous infusion or a subcutaneous injection. 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 specified in Table 1. Following the initial intravenous administration, administer an intravenous infusion at 2 and 4 weeks and every 4 weeks thereafter.

Subcutaneous Dosing Regimen

Administer 125 mg of ORENCIA subcutaneously once weekly (no intravenous loading dose is needed) [see Dosage and Administration (2.5)]. For patients switching from ORENCIA intravenous infusions to subcutaneous administration, administer the first subcutaneous dose instead of the next scheduled intravenous dose.

2.4 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 needle of the vial to reconstitute using the ORENCIA vial.

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.
ORENCIA® (abatacept)

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) Administer the entire diluted ORENCIA solution over a period of 30 minutes with an infusion set and a sterile, non-pyrogenic, low-protein-binding filter (pore size of 0.2 µm to 1.2 µm).

10) Must complete the infusion of the diluted ORENCIA solution within 24 hours of reconstitution of the ORENCIA vials.

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.

2.5 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.

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 syringe) 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

- 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)]

- Subcutaneous Use
  Injection: 50 mg/0.4 mL, 75 mg/0.6 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 Concomitant Use with 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 RA clinical trials, there was one case of a hypersensitivity reaction (0.5%) [see Adverse Reactions (6.1, 6.2)].

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

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

5.3 Infections

Serious infections, including sepsis and pneumonia, have been reported in patients receiving ORENCIA (serious infections were reported in 3% and 1.9% of RA patients treated with intravenous ORENCIA and placebo, respectively) [see Adverse Reactions (6.1)]. Some of these infections have been fatal. Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy which in addition to their underlying disease may 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 B were excluded from study.

5.4 Immunizations

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

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

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

5.6 Immunosuppression

The possibility exists for drugs inhibiting T cell activation, including ORENCIA, to affect the development and course of malignancies. 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)]. There have been reports of malignancies, including skin cancer in patients receiving ORENCIA [see Adverse Reactions (6.4)]. Periodic skin examinations are recommended for all ORENCIA-treated patients, particularly those with risk factors for skin cancer.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not predict the rates observed in a broader patient population in clinical practice.

6.1 Clinical Trials Experience in Adult Patients with RA and PsA

Adverse Reactions in Adult Patients with RA Treated with Intravenous ORENCIA

The data from placebo-controlled studies described herein reflect exposure to ORENCIA administered intravenously in patients with active RA (1955 patients with ORENCIA, 989 with placebo) [Studies I through VI] [see Clinical Studies (14.1)]. The studies had either a double-blind, placebo-controlled period of 6 months (258 patients with ORENCIA, 133 with placebo) or 1 year (1057 patients with ORENCIA, 536 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 (1.4)]. 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 anakinara.
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The most serious adverse reactions were serious infections and malignancies. The most commonly reported adverse events (occurring in ≥10% of patients treated with ORENCIA) were headache, upper respiratory tract infection, nasopharyngitis, and nausea.

The adverse reactions most frequently resulting in clinical intervention (interruption or discontinuation of ORENCIA) were due to infection. The most frequently reported infections resulting in dose interruption were upper respiratory tract infection (1%), bronchitis (0.7%), and herpes zoster (0.7%). The most frequent infections resulting in discontinuation were pneumonia (0.2%), localized infection (0.2%), and bronchitis (0.1%).

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

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

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

<table>
<thead>
<tr>
<th></th>
<th>Intravenous ORENCIA (n=1956)a</th>
<th>Placebo (n=989)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>18%</td>
<td>13%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12%</td>
<td>9%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>Cough</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>Back pain</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Rash</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>3%</td>
<td>2%</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, rhinitis, herpes simplex, and pneumonia [see Warnings and Precautions (5.3)].

Serious infections were reported in 3% of patients treated with ORENCIA and 1.9% of patients treated with placebo. The most common (0.2%-0.5%) serious infections reported with ORENCIA were pneumonia, cellulitis, urinary tract infection, bronchitis, diverticulitis, and acute pyelonephritis [see Warnings and Precautions (5.3)].

Malignancies in Adult Patients with RA Treated with Intravenous ORENCIA

In the placebo-controlled portions of the clinical trials (1955 patients treated for RA with ORENCIA for a median of 12 months), the overall frequencies of malignancies were similar in the ORENCIA- and placebo-treated patients (1.3% and 1.1%, respectively). However, more cases of lung cancer were observed in ORENCIA-treated patients (4 cases, 0.2%) than placebo-treated patients (0 cases, 0%). In the cumulative intravenous ORENCIA clinical trials in patients with RA (placebo-controlled and uncontrolled, open-label) a total of 8 cases of lung cancer (0.21 cases per 100 patient-years) and 4 lymphomas (0.10 cases per 100 patient-years) were observed in 2688 patients (3827 patient-years). The rate observed for lymphoma is approximately 3.5-fold higher than expected in an age- and gender-matched general population based on the National Cancer Institute’s Surveillance, Epidemiology, and End Results Database. Patients with RA, particularly those with highly active disease, are at a higher risk for the development of lymphoma. Other malignancies included skin, breast, bile duct, bladder, cervical, endometrial, lymphoma, melanoma, myelodysplastic syndrome, ovarian, prostate, renal, thyroid, and uterine cancers [see Warnings and Precautions (5.6)]. The potential role of ORENCIA in the development of malignancies in humans is unknown.

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

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

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

In clinical trials of 2688 adult RA patients treated with intravenous ORENCIA, there were two cases (<0.1%) of anaphylaxis. Other reactions potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, each occurred in less than 0.9% of ORENCIA-treated patients and generally occurred within 24 hours of infusion. Appropriate medical support measures for the treatment of hypersensitivity reactions should be available for immediate use in the event of a reaction [see Warnings and Precautions (5.2)].

Adverse Reactions in Patients with COPD Treated for RA with Intravenous ORENCIA

In Study V [see Clinical Studies (14.1)], there were 37 and 17 patients with chronic obstructive pulmonary disease (COPD) who were treated for RA with ORENCIA and placebo, respectively. The COPD patients treated with ORENCIA for RA developed adverse events more frequently than those treated with placebo (97% vs 88%, respectively). Respiratory disorders occurred more frequently in ORENCIA-treated patients compared to placebo-treated patients (43% vs 24%, respectively) including COPD exacerbation, cough, rhonchi, and dysnea. A greater percentage of ORENCIA-treated patients developed a serious adverse event compared to placebo-treated patients (27% vs 6%), including COPD exacerbation [3 of 37 patients (8%)] and pneumonia [1 of 37 patients (3%)] [see Warnings and Precautions (5.5)].

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

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

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

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

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

The safety of ORENCIA was evaluated in 594 patients with PsA (341 patients on ORENCIA and 253 patients on placebo), in two randomized, double-blind, placebo-controlled trials [see Clinical Studies (14.3)]. Of the 341 patients who received ORENCIA, 126 patients received intravenous ORENCIA (PsA-I) and 213 patients received subcutaneous ORENCIA (PsA-II). The safety profile was comparable between ORENCIA given intravenously in Study PsA-I and ORENCIA given subcutaneously in Study PsA-II and also consistent with the safety profile of ORENCIA in patients with RA [see Warnings and Precautions (5)].

6.2 Clinical Trials Experience in Patients with Polymicrobial Juvenile Idiopathic Arthritis

Adverse Reactions in Patients with pJIA Treated with Intravenous ORENCIA

In general, the adverse events in pediatric patients with polymicrobial 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-I was a three-part study including an open-label extension that assessed the safety profile of ORENCIA in patients with polyarticular and oligoarticular JIA. The safety experience in these patients was consistent with the pediatric experience in RA [see Clinical Studies (14.5) and Warnings and Precautions (5)].

Injection Site Reactions in Adult RA Patients Treated with Subcutaneous ORENCIA

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

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

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

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

The safety of ORENCIA was evaluated in 594 patients with PsA (341 patients on ORENCIA and 253 patients on placebo), in two randomized, double-blind, placebo-controlled trials [see Clinical Studies (14.3)]. Of the 341 patients who received ORENCIA, 126 patients received intravenous ORENCIA (PsA-I) and 213 patients received subcutaneous ORENCIA (PsA-II). The safety profile was comparable between ORENCIA given intravenously in Study PsA-I and ORENCIA given subcutaneously in Study PsA-II and also consistent with the safety profile of ORENCIA in patients with RA [see Warnings and Precautions (5)].

Adverse Reactions (6.1, 6.2)
A total of 6 serious adverse events [acute lymphocytic leukemia, ovarian cyst, varicella infection, disease flare (2), and joint wear] were reported during the initial 4 months of treatment with intravenous ORENCIA. Of the 190 pediatric patients with pJIA treated with intravenous ORENCIA in clinical trials, there was one case of a hypersensitivity reaction (0.5%). During Periods A, B, and C, acute infusion-related reactions occurred at a frequency of 4%, 2%, and 3%, respectively, and were consistent with the types of events reported in adults. Upon continued treatment in the open-label extension period, the types of adverse events were similar in frequency and type to those seen in adult patients, except for a single patient diagnosed with multiple sclerosis while on open-label treatment. 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. Twenty years of experience with pJIA. The adverse reaction profile in patients with pJIA treated with ORENCIA administered subcutaneously in Study JIA-2 were 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%. 6.3 Immunogenicity As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other abatacept products may be misleading. Immunogenicity in Adult Patients with RA Treated with Intravenous ORENCIA Antibodies directed against the entire abatacept molecule or to the CTLA-4 portion of abatacept were assessed by ELISA assays in RA patients for up to 2 years following repeated treatment with intravenous ORENCIA. Thirty-four of 1993 (2%) patients developed binding antibodies to the entire abatacept molecule or to the CTLA-4 portion of abatacept. Because trough levels of abatacept can interfere with assay results, a subset analysis was performed. In the subset analysis, 9 of 154 (6%) patients that had discontinued intravenous ORENCIA treatment for over 56 days developed antibodies. Samples with confirmed binding activity to CTLA-4 were assessed for the presence of neutralizing antibodies in a cell-based luciferase reporter assay. Six of 9 (67%) evaluable patients were shown to possess neutralizing antibodies. However, the development of neutralizing antibodies may be underreported due to lack of assay sensitivity. No correlation of anti-abatacept antibody development to clinical response or adverse events was observed. Immunogenicity in Adult RA Patients Treated with Subcutaneous or Intravenous ORENCIA Study SC-1 compared the immunogenicity to abatacept following subcutaneous or intravenous ORENCIA administration. The overall immunogenicity frequency to abatacept was 1% (8/725) and 2% (16/710) for the subcutaneous and intravenous groups, respectively. The rate is consistent with previous experience, and there was no correlation of immunogenicity with effects on pharmacokinetics, safety, or efficacy. Immunogenicity in Adult RA Patients Treated with Subcutaneous ORENCIA Monotherapy Study SC-2 was conducted to determine the effect of subcutaneous monotherapy use of ORENCIA on immunogenicity (without an intravenous loading dose) in 100 RA patients, who had not previously received ORENCIA or other CTLA4ig. Patients in this study received either subcutaneous ORENCIA plus methotrexate (n=51) or subcutaneous ORENCIA monotherapy (n=49). No patients in either group developed anti-abatacept antibodies after 4 months of treatment. The safety observed in this study was consistent with that observed in the other subcutaneous studies. Immunogenicity in Adult RA Patients After Treatment, Withdrawal, and then Restart of Subcutaneous ORENCIA Study SC-3 was conducted to investigate the immunogenicity in adult RA patients after treatment, withdrawal (three months), and restart of ORENCIA subcutaneous treatment (patients were treated concomitantly with methotrexate). One hundred sixty-seven patients were enrolled in the first 3-month treatment period and responders (n=120) were randomized to either subcutaneous ORENCIA or placebo for the second 3-month period (withdrawal period). Patients from this period then received open-label ORENCIA treatment in the final 3-month period of the study (period 3). At the end of the withdrawal period, 0/38 (0%) patients who continued to receive subcutaneous ORENCIA developed anti-abatacept antibodies compared to 7/773 (10%) of patients who had subcutaneous ORENCIA withdrawn during the period. Half of the patients who received subcutaneous ORENCIA placebo during the withdrawal period received a single intravenous infusion of ORENCIA at the start of period 3 and half received intravenous placebo. At the end of period 3, when all patients again received subcutaneous ORENCIA, the immunogenicity rates were 1/38 (3%) in the group who received subcutaneous ORENCIA throughout, and 2/73 (3%) in the group that had received placebo during the withdrawal period. Upon reinitiating therapy, there were no injection reactions and no differences in response to therapy in patients who were withdrawn from subcutaneous therapy for up to 3 months compared to those who remained on subcutaneous therapy (these results occurred in those who received or did not receive an intravenous loading dose). The safety observed in this study was consistent with that observed in the other studies. Immunogenicity in Patients with pJIA 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 pJIA following repeated treatment with intravenous ORENCIA throughout the open-label period. For patients who were withdrawn from therapy for up to 6 months during the double-blind period, the rate of antibody formation to the CTLA-4 portion of the molecule was 41% (22/54), while for those who remained on therapy the rate was 13% (7/54). Twenty of these patients had samples that could be tested for antibodies with neutralizing activity; of these, 8 (40%) patients were shown to possess neutralizing antibodies. The presence of antibodies was generally transient, and titers were low. The presence of antibodies was not associated with adverse events, changes in efficacy, or an effect on serum concentrations of abatacept. For patients who were withdrawn from ORENCIA during the double-blind period for up to 6 months, no serious acute infusion-related events were observed upon re-initiation of ORENCIA therapy. 6.4 Postmarketing Experience Adverse reactions have been reported during the postapproval use of ORENCIA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to ORENCIA. Based on the postmarketing experience with ORENCIA, the following adverse reactions have been identified: • Vasculitis (including cutaneous vasculitis and leukocytoclastic vasculitis) • New or worsening psoriasis • Non-melanoma skin cancers (basal cell carcinoma and squamous cell carcinoma) • Angioedema reactions [see Warnings and Precautions (5.2)] During postmarketing experience with intravenous ORENCIA, systemic infusion reactions were similar to that seen in the clinical trial experience with intravenous ORENCIA with the exception of one case of fatal anaphylaxis [see Warnings and Precautions (5.2)]. Postmarketing reports of systemic injection reactions (e.g., pruritus, throat tightness, dyspnea) have occurred following the use of subcutaneous ORENCIA. 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)]. 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 pyruvoleinite quinone (GDH-POQ). The GDH-POQ 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.
the maximum recommended human dose (MRHD) of 10 mg/kg/month on an AUC basis. However, in a pre- and postnatal development study in rats, ORENCIA altered immune function in female rats at 11 times the MRHD on an AUC basis.

Data

Human Data

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

Animal Data

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

In a study of pre- and postnatal development in rats (10, 45, or 200 mg/kg every 3 days from gestation day 6 through lactation day 21), alterations in immune function in female offspring, consisting of a 9-fold increase in T-cell-dependent antibody response relative to controls on postnatal day (PND) 56 and thyroiditis in a single female pup on PND 112, occurred at approximately 11 times the MRHD on an AUC basis (at a maternal dose of 200 mg/kg/day). No adverse effects were observed at approximately 3 times the MRHD (a maternal dose of 45 mg/kg). It is not known if immunologic perturbations in rats are relevant indicators of a risk for development of autoimmune diseases in humans exposed in utero to abatacept. Exposure to abatacept in the juvenile rat, which may be more representative of the fetal immune system state in the human, resulted in immune system abnormalities including inflammation of the thyroid and pancreas [see Nonclinical Toxicology (13.2)].

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

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

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 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 efficacy of ORENCIA in pediatric patients for uses other than pJIA have not been established. The safety and effectiveness of ORENCIA in pediatric patients less than two years old has not been established.

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

Juvenile Animal Toxicity Data

A juvenile animal study conducted in rats dosed with abatacept from 4 to 94 days of age (prior to immune system maturity) showed an increase in the incidence of infections leading to death at all doses compared with controls. Altered T-cell subsets including increased T-helper cells and reduced T-regulatory cells were observed. In addition, inhibition of T-cell-dependent antibody responses (TDAR) was observed. Upon following these animals into adulthood, lymphocytic inflammation of the thyroid and pancreatic islets was observed. In contrast, studies in adult mice and monkeys have not demonstrated similar findings. As the immune system of the rat is undeveloped in the first few weeks after birth, the relevance of these results to humans is unknown.

8.5 Geriatric Use

A total of 323 patients 65 years of age and older, including 53 patients 75 years and older, received ORENCIA in clinical studies. No overall differences in safety or effectiveness were observed between 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.

10 OVERDOSAGE

Doses up to 50 mg/kg (5 times the maximum recommended dose) have been administered intravenously without apparent toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

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 kilodaltons.

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 (4.6 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 4).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

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

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 5).

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Healthy Subjects (After 10 mg/kg Single Dose)</th>
<th>RA Patients (After 10 mg/kg Multiple Dosesa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Concentration (Cmax) [mcg/mL]</td>
<td>292 (175-427)</td>
<td>295 (171-398)</td>
</tr>
<tr>
<td>Terminal half-life (t1/2) [days]</td>
<td>16.7 (12-23)</td>
<td>13.1 (8-25)</td>
</tr>
<tr>
<td>Systemic clearance (CL) [ml/h/kg]</td>
<td>0.23 (0.16-0.30)</td>
<td>0.22 (0.13-0.47)</td>
</tr>
<tr>
<td>Volume of distribution (Vss) [L/kg]</td>
<td>0.09 (0.06-0.13)</td>
<td>0.07 (0.02-0.13)</td>
</tr>
</tbody>
</table>

* Multiple intravenous infusions of ORENCIA were administered at days 1, 15, 30, and monthly thereafter.

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

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

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

Adult RA - Subcutaneous Administration
Abatacept exhibited linear pharmacokinetics following subcutaneous administration. The mean (range) for Cmax and CLmax at steady state observed after 85 days of treatment was 32.5 mcg/mL (6.6 to 113.8 mcg/mL) and 48.1 mcg/mL (9.8 to 132.4 mcg/mL), respectively. The bioavailability of abatacept following subcutaneous administration relative to intravenous administration was 79%. Mean estimates for systemic clearance (0.28 ml/h/kg), volume of distribution (0.11 L/kg), and terminal half-life (14.3 days) were comparable between subcutaneous and intravenous administration.

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

Consistent with the intravenous data, population pharmacokinetic analyses for subcutaneous ORENCIA in RA patients revealed that there was a trend toward higher clearance (L/h) of abatacept with increasing body weight [see Dosage and Administration (2.2)]. In addition, relative to the RA patients with the same body weight, abatacept clearance in PaA patients was approximately 8% lower, resulting in higher abatacept exposures in patients with PaA. This slight difference in exposures, however, is not considered to be clinically meaningful.

13 NONCLINICAL TOXICOLOGY

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

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

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

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

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

Polycystic 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 85 following the weekly body-weight–titered subcutaneous ORENCIA dosing [see Clinical Studies (14.2)]. Comparable trough concentrations across weight tiers and age groups were achieved by the body-weight–titered 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). 46.6 mcg/mL (22.4 to 97.0 mcg/mL), and 38.5 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 JIA patients revealed that there was a trend toward higher clearance of abatacept with increasing body weight [see Dosage and Administration (2.2)]. 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.

Adult Psoriatic Arthritis - Intravenous and Subcutaneous Administration
In Study PaA-1, a dose ranging study, intravenous ORENCIA was administered at 3 mg/kg, weight range-based dosing: 500 mg for patients weighing less than 60 kg, 750 mg for patients weighing 60 to 100 kg, and 1000 mg for patients weighing greater than 100 kg, or doses of 30 mg/kg on Days 1 and 15 followed by weight-range-based dosing [see Clinical Studies (14.3)]. Following monthly intravenous ORENCIA administration, abatacept showed linear PK over the dose range in this study. At the weight-range-based dosing (see above), the steady state of abatacept was reached by Day 57 and the geometric mean (CV%) trough concentration (Cmin) was 24.3 mcg/mL (40.8%) at Day 169. In Study PaA-4 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 PaA patients revealed that there was a trend to 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 PaA patients was approximately 8% lower, resulting in higher abatacept exposures in patients with PaA. This slight difference in exposures, however, is not considered to be clinically meaningful.
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 (see 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; up to three ACR responses, all DMARDs, and all corticosteroids were permitted.
- In Study VI, the efficacy and safety of ORENCIA were assessed in 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.

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

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

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

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

Clinical Response 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 6. ORENCIA-treated patients had higher ACR 20, 50, and 70 response rates at 6 months compared to placebo-treated patients. Month 6 ACR response rates in Study II for the 10 mg/kg group were similar to the ORENCIA group in Study III.

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

In Study VI, a greater proportion of patients treated with ORENCIA plus MTX achieved a low level of disease activity as measured by a DAS28-CRP less than 2.6 at 12 months compared to those treated with MTX plus placebo (Table 6). 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 6, 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 6. 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).
ORENcia® (abatacept)

Table 7: Components of ACR Responses at 6 Months in Adult Patients with RA

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ORENCIA® (n=256)</th>
<th>Placebo/MTX (n=255)</th>
<th>Differences</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tender joints</td>
<td>30%</td>
<td>31%</td>
<td>1%</td>
<td>0.39</td>
</tr>
<tr>
<td>SJC</td>
<td>31%</td>
<td>32%</td>
<td>1%</td>
<td>0.39</td>
</tr>
<tr>
<td>DAS28</td>
<td>5%</td>
<td>6%</td>
<td>1%</td>
<td>0.19</td>
</tr>
<tr>
<td>HAQ-DI (modified)</td>
<td>0.2</td>
<td>0.3</td>
<td>0.1</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Study SC-1 is a non-inferiority study. Per protocol data is presented in table.

In the open-label extension of Study III, 75% of patients initially randomized to ORENCIA/MTX and 65% of patients initially randomized to placebo/MTX were evaluated radiographically at Year 2. As shown in Table 8, progression of structural damage in ORENCIA/MTX-treated patients was further reduced in the second year of treatment.

Physical Function Response and Health-Related Outcomes in Adult RA Patients

In the open-label extension of Study III, 75% of patients initially randomized to ORENCIA/MTX and 65% of patients initially randomized to placebo/MTX were evaluated radiographically at Year 2. As shown in Table 8, progression of structural damage in ORENCIA/MTX-treated patients was further reduced in the second year of treatment.

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

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.

In the open-label extension of Study III, 75% of patients initially randomized to ORENCIA/MTX and 65% of patients initially randomized to placebo/MTX were evaluated radiographically at Year 2. As shown in Table 8, progression of structural damage in ORENCIA/MTX-treated patients was further reduced in the second year of treatment.

In Study III and Study VI, structural joint damage was assessed radiographically and expressed as change from baseline in the Genant-modified Total Sharp Score (TSS) and its components, the Erosion Score (ES) and Joint Space Narrowing (JSN) score. ORENCIA/MTX slowed the progression of structural damage compared to placebo/MTX after 12 months of treatment as shown in Table 8.
ORENCIA® (abatacept)

14.2 Polyarticular Juvenile Idiopathic Arthritis

The safety and efficacy of ORENCIA with intravenous administration were assessed in Study JIA-1, a three-arm study including an open-label extension in pediatric patients with polyarticular juvenile idiopathic arthritis (pJIA). Patients 6 to 17 years of age (n=190) with moderately to severely active pJIA who had an inadequate response to one or more DMARDs, such as MTX or TNF antagonists, were treated. Patients had a disease duration of approximately 4 years with moderately to severely active disease at study entry, as determined by baseline counts of active joints (mean, 16) and joints with loss of motion (mean, 16); patients had elevated C-reactive protein (CRP) levels (mean, 3.2 mg/dL) and ESR (mean, 32 mm/h). The patients enrolled had JIA subtypes that at disease onset included polyarticular (16%), psoriatic (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 1000 mg per dose) intravenously on days 1, 15, 29, and monthly thereafter. Response was assessed utilizing the ACR Pediatric 30 definition of improvement, defined as ≥30% improvement in at least 3 of the 6 JIA core set variables and ≥30% worsening in not more than 1 of the 6 JIA core set variables. Patients demonstrating an ACR Pedi 30 response at the end of Period A were randomized into the double-blind phase (Period B) and received either ORENCIA or placebo for 6 months or until disease flare. Disease flare was defined as a ≥30% worsening in at least 3 of the 6 JIA core set variables with ≥30% improvement in not more than 1 of the 6 JIA core set variables; ≥2 cm of worsening of the Physician or Parent Global Assessment was necessary if used as 1 of the 3 JIA core set variables used to define flare, and worsening in ≥2 joints was necessary if the number of active joints or joints with limitation of motion was used as 1 of the 3 JIA core set variables used to define flare.

At the conclusion of Period A, pediatric ACR 30/50/70 responses were 65%, 50%, and 28%, respectively. Pediatric ACR 30 responses were similar in all subtypes of JIA studied. During the double-blind randomized withdrawal phase (Period B), ORENCIA-treated patients (intravenous) experienced significantly fewer disease flares compared to placebo-treated patients (20% vs 53%); 95% CI of the difference (15%, 52%). The risk of disease flare among patients continuing on intravenous ORENCIA was less than one-third than that for patients withdrawn from intravenous ORENCIA treatment (hazard ratio=0.31, 95% CI [0.16, 0.59]). Among patients who received intravenous ORENCIA throughout the study (Period A, Period B, and the open-label extension Period C), the proportion of pediatric ACR 30/50/70 responders remained consistent for 1 year.

Table 10: Proportion of Patients With ACR Responses at Week 24 in Studies PsA-I and PsA-II

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>ORENCIA 50 mg</th>
<th>ORENCIA 75 mg</th>
<th>ORENCIA 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR 20</td>
<td>19.0%</td>
<td>19.0%</td>
<td>39.4%</td>
<td>22.3%</td>
</tr>
<tr>
<td>ACR 50</td>
<td>24.0%</td>
<td>24.0%</td>
<td>19.2%</td>
<td>12.3%</td>
</tr>
<tr>
<td>ACR 70</td>
<td>12.5%</td>
<td>0.0%</td>
<td>10.3%</td>
<td>6.6%</td>
</tr>
</tbody>
</table>

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

**Figure 2:** Percent of Patients Achieving ACR20 Responsea in PsA-II Study Through Week 24 (Day 169)

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

In PsA-II, 424 patients were randomized 1:1 to receive weekly doses of subcutaneous placebo or ORENCIA 125 mg without a loading dose for 24 weeks-in a double-blind manner, followed by open-label subcutaneous ORENCIA 125 mg weekly. Patients were allowed to receive stable doses of concomitant MTX, sulfasalazine, leflunomide, hydroxychloroquine, low dose corticosteroids (equivalent to ≤10 mg of prednisone) and/or NSAIDs during the trial. At randomization, 60% of patients were receiving MTX. The baseline disease characteristics included presence of joint erosion on X-rays in 84% (341/407) with a mean (SD) PsA-modified Sharp van der Heijde erosion score (SHS) of 10.8 (24.2), elevated serum C reactive protein (CRP) in 66% [277/421] with a mean (SD) of 14.1 mg/L (25.9), and psoriatic arthritis 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 the ACR20 response after treatment with subcutaneous 125 mg compared to placebo in Study PsA-II at Week 24. Responses were regarded as non-significant for treatment with ORENCIA.

### Table 10: Proportion of Patients With ACR Responses at Week 24 in Studies PsA-I and PsA-II

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>ORENCIA 50 mg</th>
<th>ORENCIA 75 mg</th>
<th>ORENCIA 100 mg</th>
</tr>
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<tr>
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<td>20%</td>
</tr>
<tr>
<td>ACR 50</td>
<td>15%</td>
<td>20%</td>
<td>30%</td>
<td>20%</td>
</tr>
<tr>
<td>ACR 70</td>
<td>10%</td>
<td>5%</td>
<td>10%</td>
<td>5%</td>
</tr>
</tbody>
</table>

* p<0.05 versus placebo.

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

Results were generally consistent across the ACR components in Study PsA-I and PsA-II. Improvements in enthesis and dactylitis were seen with ORENCIA treatment at Week 24 in both PsA-I and PsA-II.
ORENCIA® (abatacept) injection and ORENCIA® ClickJect (abatacept) injection are clear, silicone-free disposable syringes, providing 250 mg of abatacept: vial (one may use less than the full contents of the vial or use more than one vial) with a passive™ needle guard and flange extenders.

For Subcutaneous Use
ORENCIA® (abatacept) for injection is a white lyophilized powder for intravenous infusion supplied as single-dose disposable prefilled glass syringes with BD UltraSafe™ needle guard and flange extenders. The prefilled 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
ORENCIA® (abatacept) injection and ORENCIA® ClickJect (abatacept) injection are clear to slightly opalescent, colorless to pale yellow solutions for subcutaneous administration.

Prefilled Syringe
ORENCIA (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.

ClickJect Autoinjector
ORENCIA (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 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 0003-2187-51: 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION
Advises the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

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
Instruct 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.
**ORENCIA® (abatacept)**

**PATIENT INFORMATION**

**ORENCIA® (oh-REN-see-ah)**
(abatacept)
for injection, for intravenous use

**ORENCIA® (oh-REN-see-ah)**
(abatacept)
injection, for subcutaneous use

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**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.
- patients 2 years of age and older with moderate to severe polyarticular juvenile idiopathic arthritis (JIA). 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.

It is not known if ORENCIA is safe and effective in children under 2 years of age.

It is not known if ORENCIA is safe and effective in children for uses other than juvenile idiopathic arthritis.

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**Before you 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 when taking 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). Before you use ORENCIA, your healthcare provider may examine you for hepatitis.
- 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. Before you use ORENCIA, your healthcare provider may examine you for TB or perform a skin test. Symptoms of TB may include:
  - a cough that does not go away
  - fever
  - weight loss
  - night sweats
- 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 taking 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.
- 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 to treat RA, JIA or PsA that may affect your immune system, such as:

- **Enbrel®** (etanercept)
- **Humira®** (adalimumab)
- **Remicade®** (infliximab)
- **Kineret®** (anakinra)
- **Rituxan®** (rituximab)
- **Cimzia®** (certolizumab pegol)
- **Actemra®** (tocilizumab)
- **Simponi®** (golimumab)

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

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 should I use ORENCIA?

- **You may receive ORENCIA given by a healthcare provider through a vein in your arm (IV or 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.**

### 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 use 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 while you use 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
  - cough
  - trouble breathing
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.

**Common side effects of ORENCIA include:**
- headache
- upper respiratory tract infection
- sore throat
- nausea

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

These are not all 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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Princeton, NJ 08543 USA, U.S. License Number 1713

All other trademarks are property of their respective owners.
For more information, go to www.ORENCIA.com or call 1-800-ORENCIA.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised June 2020
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**

- **Viewing window**
- **Plunger**
- **Needle cover**
- **Expiration date**
- **Flange extender**

**After Use**

- **Needle guard (extended over needle)**
- **Flange extender**

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
Step 1: Preparing for an ORENCIA 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.
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.
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](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.
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.

Bristol-Myers Squibb Company
Princeton, NJ 08543 USA, U.S. License Number 1713

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Revised March 2017

INSTRUCTIONS FOR USE
ORENCIA® ClickJect™ (oh-REN-see-ah)
(abatacept)
Prefilled Autoinjector
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

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 90º 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.

**Cotton ball or gauze**

**Adhesive bandage**

Continued on Next Page
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.
Frequently Asked Questions (Continued)

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.

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