

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr **ORENCIA**[®]

abatacept for injection

Lyophilized powder for solution for infusion (250 mg/vial)

Professed Standard

Pr **ORENCIA**[®]

abatacept for injection

Solution for subcutaneous injection (125 mg/mL)

Professed Standard

Selective Co-stimulation Modulator

Bristol-Myers Squibb Canada
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Montreal, Quebec
H4S 0A4

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1 INDICATIONS, 1.1 Pediatrics	07/2022
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Adult Rheumatoid Arthritis (RA)

ORENCIA (abatacept) is indicated in the treatment of Rheumatoid Arthritis for:

1. reducing signs and symptoms
2. inducing clinical responses

ORENCIA may be also used long-term, to inhibit the progression of structural damage, and improve physical function in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs or to TNF antagonists or to both.

ORENCIA may be administered by Intravenous (IV) or Subcutaneous (SC) route (see [4 DOSAGE AND ADMINISTRATION](#)). It is expected, based on Pharmacokinetic information, that the SC route of administration for ORENCIA will be beneficial in the long-term (See [10 CLINICAL PHARMACOLOGY](#)).

ORENCIA may be used as monotherapy or in combination with DMARD therapy.

When used as first-line treatment in recently diagnosed patients who have not been previously treated with methotrexate (MTX), ORENCIA should be given in combination with MTX.

Juvenile Idiopathic Arthritis (JIA)/Juvenile Rheumatoid Arthritis (JRA)

ORENCIA **administered by intravenous (IV) infusion** is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis/juvenile rheumatoid arthritis in pediatric patients 6 years of age and older who have had an inadequate response to one or more DMARDs, such as MTX.

ORENCIA **administered by intravenous (IV) infusion** has not been studied in children less than 6 years of age.

No data for the SC injection in children are available to Health Canada; therefore, Health Canada has not authorized an indication for SC pediatric use.

Adult Psoriatic Arthritis (PsA)

ORENCIA is indicated for the treatment of adult patients with active psoriatic arthritis (PsA) when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.

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

Prophylaxis for Acute Graft versus Host Disease

ORENCIA is indicated for the prophylaxis of moderate to severe acute graft versus host disease (aGVHD), in combination with a calcineurin inhibitor and methotrexate, in adults and pediatric patients 6 years of age and older undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated donor.

1.1 Pediatrics (6 years of age and older)

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of ORENCIA in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use (see [1 INDICATIONS](#)).

ORENCIA is indicated for the treatment of pediatric patients with:

- juvenile idiopathic arthritis/juvenile rheumatoid arthritis
- prophylaxis of moderate to severe acute graft versus host disease (aGVHD) in unrelated-donor hematopoietic stem cell transplantation (HSCT)

1.2 Geriatrics

Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety.

2 CONTRAINDICATIONS

ORENCIA (abatacept) should not be administered to

- Patients with known hypersensitivity to ORENCIA or any of its components.
- Patients with, or at risk of, sepsis syndrome, such as immunocompromised and HIV+ patients (see [7 WARNINGS AND PRECAUTIONS](#)).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Hypersensitivity

- In post-marketing experience, a case of fatal anaphylaxis following the first infusion of ORENCIA has been reported (see [7 WARNINGS AND PRECAUTIONS](#)).

Infections

- Treatment with ORENCIA should not be initiated in patients with active infections including chronic or localized infections.
- Treatment with ORENCIA also should not be initiated in patients with chronic or latent infections.
- Administration of ORENCIA should be discontinued if a patient develops a serious infection.
- Physicians should exercise caution when considering the use of ORENCIA in patients with a history of recurrent infection or underlying conditions which may predispose them to infections, such as immunodeficiency disorders, or who have resided in regions where tuberculosis and histoplasmosis are endemic.
- If active tuberculosis is diagnosed, ORENCIA therapy should not be initiated. If inactive ('latent') tuberculosis is diagnosed, treatment for latent tuberculosis should be started with anti-tuberculosis therapy before the initiation of ORENCIA.
- Physicians should monitor patients receiving ORENCIA for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis infection.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

General Considerations for Subcutaneous Administration

- ORENCIA Injection, 125 mg pre-filled syringe is not intended for IV infusion.
- ORENCIA Injection is intended for use under the guidance of a healthcare professional. After proper training in subcutaneous injection technique, a patient may self inject with ORENCIA if a healthcare professional determines that it is appropriate. Patients should be instructed to follow the directions provided in the “Patient/Caregivers Instructions for Use” for additional details on medication administration.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use ORENCIA prefilled syringes exhibiting particulate matter or discoloration. ORENCIA should be clear and colorless to pale yellow. Any leftover product remaining in the prefilled syringe should not be used.
- Patients using ORENCIA for subcutaneous administration should be instructed to inject the full amount in the syringe (1.0 mL), which provides 125 mg of ORENCIA, according to the directions provided in the Patient Information leaflet and the “Patient/Caregivers Instructions for Use”.
- Injection sites should be rotated and injections should never be given into areas where the skin is tender, bruised, red, or hard.

4.2 Recommended Dose and Dosage Adjustment

Adult Psoriatic Arthritis

Intravenous Dosing Regimen

ORENCIA IV should be administered as a 30-minute intravenous infusion utilizing the weight range-based dosing specified in

Table 2. Following the initial intravenous administration, an intravenous infusion should be given at 2 and 4 weeks after the first infusion and every 4 weeks thereafter.

Subcutaneous Dosing Regimen

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

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

Available data suggest that the clinical response is usually achieved within 16 weeks of treatment.

Discontinuation of treatment should be considered in a patient not responding within this time period.

Juvenile Idiopathic Arthritis/Juvenile Rheumatoid Arthritis

Intravenous Infusion

For pediatric and adolescent patients with juvenile idiopathic arthritis (JIA)/juvenile rheumatoid arthritis (JRA), a dose specifically calculated based on each patient's body weight is used.

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

Prophylaxis for Acute Graft versus Host Disease

Antiviral Prophylactic treatment

Before administering ORENCIA, administer recommended antiviral prophylactic treatment for Epstein-Barr Virus (EBV) reactivation, and continue for six months following HSCT. In addition, consider prophylactic antivirals for Cytomegalovirus (CMV) infection/reactivation during treatment and for six months following HSCT (see [7 WARNINGS AND PRECAUTIONS](#)).

Intravenous Dosing Regimen

Administer ORENCIA 10 mg/kg dose (maximum dose of 1,000 mg) as an intravenous infusion over 60-minutes on the day before transplantation (Day -1), followed by administration on Day 5, 14, and 28 after transplantation.

Any unused portions in the vials must be immediately discarded.

4.3 Reconstitution

Parenteral Products:

Preparation and Administration Instructions for Intravenous Infusion

Use aseptic technique.

ORENCIA is provided as a lyophilized powder in preservative-free, single-use vials. Each vial of ORENCIA must be reconstituted with 10 mL of Sterile Water for Injection, USP. After reconstitution, the concentration of abatacept in the vial will be 25 mg/mL. Immediately after reconstitution, the product must be further diluted to 100 mL with 0.9% Sodium Chloride Injection, USP. The infusion of the fully diluted ORENCIA solution must be completed within 24 hours of preparation. The fully diluted ORENCIA solution may be stored at room temperature or refrigerated at 2° -8° C before use.

Table 1: Reconstitution

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Concentration per mL
15 mL	10 mL Sterile Water for Injection, USP	10 mL	25 mg/mL

- 1) Each ORENCIA vial provides 250 mg of abatacept for administration.
- 2) Reconstitute the ORENCIA powder in each vial with 10 mL of Sterile Water for Injection, USP, using a SILICONE-FREE DISPOSABLE SYRINGE PROVIDED WITH EACH VIAL and a 18-21-gauge needle. Remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of Sterile Water for Injection, USP, to the glass wall of the vial. Do not use the vial if the vacuum is not present. To minimize foam formation in solutions of ORENCIA, the vial should be rotated with gentle swirling until the contents are completely dissolved. **As with any protein, prolonged or vigorous agitation should be avoided. DO NOT SHAKE.** Upon complete dissolution of the lyophilized powder, the vial should be vented with a needle to dissipate any foam that may be present.

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

- 3) The reconstituted ORENCIA solution must be further diluted to 100 mL as follows. From a 100 mL infusion bag or bottle, withdraw a volume of 0.9% Sodium Chloride Injection, USP equal to the volume of the reconstituted ORENCIA solution required for the patient's dose. Slowly add the reconstituted ORENCIA solution to the infusion bag or bottle using a SILICONE-FREE DISPOSABLE SYRINGE PROVIDED WITH EACH VIAL. Gently mix. DO NOT SHAKE THE BAG OR BOTTLE. The final concentration of abatacept in the bag or bottle will depend upon the amount of drug added, but will be no more than 10 mg/mL.
- 4) Prior to administration, parenteral drug products should be inspected visually for particulate matter and discoloration whenever solution and container permit. The solution should be clear, colorless to pale yellow. Do not use if opaque particles, discoloration, or other foreign particles are present.
- 5) The entire, fully diluted ORENCIA solution should be administered over a period of 30 minutes and must be administered with an infusion set and a sterile, non-pyrogenic, LOW-PROTEIN-BINDING FILTER (pore size of 1.2 µm or less).
- 6) ORENCIA should not be infused concomitantly in the same intravenous line with other agents. No physical biochemical compatibility studies have been conducted to evaluate the co-administration of ORENCIA with other agents.

4.4 Administration

Adult Rheumatoid Arthritis

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

ORENCIA may be used as monotherapy or concomitantly with DMARDs.

Intravenous Infusion for Adult Rheumatoid Arthritis

ORENCIA IV should initially be administered as a 30-minute intravenous infusion utilizing the weight range-based dosing specified in

Table 2. Following the initial IV infusion, an intravenous infusion should be administered at 2 and 4 weeks after the first infusion and every 4 weeks thereafter.

Table 2: Dose of ORENCIA for Intravenous Infusion in Adult RA

Body Weight of Patient	Dose	Number of Vials ^a
< 60 kg	500 mg	2
60 to 100 kg	750 mg	3
> 100 kg	1 gram	4

^a Each vial provides 250 mg of abatacept for infusion.

Subcutaneous Administration for Adult Rheumatoid Arthritis

For ORENCIA-naïve patients, following a single IV loading dose as per

Table 2, the first 125 mg subcutaneous injection of ORENCIA (regardless of weight), should be given within a day followed by once-weekly subcutaneous injections at the fixed dose of 125 mg SC (see [10.3 Pharmacokinetics](#)) in addition to their MTX regimen.

Patients who are unable to receive an infusion may initiate weekly injections of subcutaneous ORENCIA without an intravenous loading dose.

Patients switching from ORENCIA intravenous therapy to subcutaneous administration should administer the first subcutaneous dose instead of the next scheduled intravenous dose in addition to their MTX regimen.

4.5 Missed Dose

If you miss your appointment or if you forget to receive your ORENCIA injection, ask your doctor when to schedule your next dose.

5 OVERDOSAGE

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medical Ingredients
Intravenous Infusion (IV)	lyophilized powder for solution 250 mg / 15 mL vial	maltose, sodium chloride, sodium phosphate monobasic Sterile Water for Injection
Subcutaneous Injection (SC)	Single-dose, disposable prefilled Syringes with BD	dibasic sodium phosphate anhydrous, monobasic sodium phosphate monohydrate,

	UltraSafe Passive™ Needle Guard with Flange Extenders 125 mg/mL	poloxamer 188, sucrose, and up to 1 mL water for injection. ORENCIA injection for subcutaneous administration contains no maltose.
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Lyophilized Powder for Intravenous Infusion

ORENCIA (abatacept) lyophilized powder for intravenous infusion is supplied as an individually packaged, single-use vial with a silicone-free disposable syringe. Each 15-mL vial contains 250 mg of abatacept.

ORENCIA lyophilized powder for IV Infusion is supplied as a sterile, white, preservative-free, lyophilized powder for intravenous infusion. Following reconstitution of the lyophilized powder with 10 mL of Sterile Water for Injection, USP, the solution of ORENCIA is clear, colorless to pale yellow, with a pH range of 7.0 to 8.0.

Solution for Subcutaneous Administration

ORENCIA Injection, solution for subcutaneous administration, is supplied as a sterile, preservative-free, ready-to-use solution for subcutaneous injection. The drug product for subcutaneous injection is supplied in:

- **Single-dose, disposable Prefilled Syringes with BD UltraSafe Passive™ Needle Guard with Flange Extenders for Subcutaneous Administration**

Each single-dose disposable prefilled glass syringe with passive needle guard with flange extenders contains 125 mg of abatacept per 1.0 mL of solution. Cartons of 1 and 4.

The Type I glass syringe has a coated stopper and fixed stainless-steel needle (5 bevel, 29-gauge thin wall, ½-inch needle) covered with a rigid needle shield.

A sufficient excess of abatacept is incorporated into each pre-filled syringe. The subcutaneous solution is clear, colorless to pale yellow with a pH of 6.8 to 7.4. Each single dose of subcutaneous injection provides 125 mg abatacept, 170 mg sucrose, 8 mg poloxamer 188, 0.286 mg monobasic sodium phosphate monohydrate, 0.838 mg dibasic sodium phosphate anhydrous, and up to 1 mL water for injection. ORENCIA injection for subcutaneous administration contains no maltose.

7 WARNINGS AND PRECAUTIONS

Please see [3 SERIOUS WARNINGS AND PRECAUTIONS BOX](#).

General

Information for Patients

Patients should be provided with Part III Patient Medication Information of this Product Monograph. Caution should be exercised in administering ORENCIA to patients with clinically important active infections and patients should be assessed accordingly prior to the administration of ORENCIA.

Carcinogenesis and Mutagenesis

The potential role of ORENCIA in the development of malignancies and lymphomas in humans is unknown. The frequencies of malignancies in the placebo-controlled clinical trials in patients with adult RA were similar for ORENCIA and placebo treated patients (1.2% and 0.9% respectively). There were no

studies conducted to date to evaluate the benefit and risk profile of ORENCIA in patients with existing malignancies or a history of lymphoma.

In clinical trials in adult RA patients, the incidence of malignant neoplasms did not appear to increase in the open-label period compared to the double-blind period (see [8 ADVERSE REACTIONS](#)).

Non-melanoma skin cancers have been reported in patients receiving abatacept. Periodic skin examinations are recommended for all patients, particularly those with risk factors for skin cancer.

Hematologic

Blood Glucose Testing

The glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) based glucose monitoring systems may react with the maltose present in ORENCIA for intravenous infusion, resulting in falsely elevated blood glucose readings on the day of infusion. When receiving ORENCIA through intravenous infusion, patients that require blood glucose monitoring should be advised to consider methods that do not react with maltose (see [9.7 Drug-Laboratory Test Interactions](#)).

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

Hepatic /Biliary/Pancreatic

ORENCIA has not been studied in these patient populations. No dose recommendations can be made (see [10.3 Pharmacokinetics](#)).

Immune

Combination with Biologic Rheumatoid Arthritis Therapy

Concurrent therapy with ORENCIA (abatacept) and a biologic RA agent is not recommended. While transitioning from biologic RA therapy to ORENCIA therapy, patients should be monitored for signs of infection. There is limited experience with the use of ORENCIA in combination with biologic RA agents (i.e., adalimumab, anakinra, etanercept, infliximab). In controlled clinical trials, compared to patients treated with biologic RA agents and placebo, patients with adult RA receiving combination biologic RA therapy with ORENCIA experienced an increase in overall infections (63.7% vs 43.3%) and serious infections (4.4% vs 1.5%). These studies did not provide sufficient data to complete a benefit and risk assessment of combination of ORENCIA with biologic rheumatoid arthritis agents. There is insufficient experience to assess the safety and efficacy of ORENCIA administered concurrently with anakinra, and therefore such use is not recommended.

Hypersensitivity

As with any other biologic RA therapy, patients should be monitored for allergic reactions. Such reactions have been observed with ORENCIA. In clinical trials with ORENCIA, patients were not pretreated to prevent hypersensitivity reactions. In patients treated with ORENCIA in the controlled double blind and cumulative periods, the events of hypersensitivity, anaphylaxis, and drug hypersensitivity were rarely reported. Other events potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, that occurred within 24 hours of ORENCIA infusion, were uncommon. Medications for the treatment of hypersensitivity reactions (e.g., acetaminophen, antihistamines, corticosteroids, and/or

epinephrine) should be available for immediate use in the event of a reaction (see [8 ADVERSE REACTIONS](#)). Anaphylaxis or anaphylactoid reactions can occur after the first infusion and can be life-threatening. In post-marketing experience, a case of fatal anaphylaxis following the first infusion of ORENCIA has been reported. If an anaphylactic or other serious allergic reaction occurs, administration of IV or SC ORENCIA should be stopped immediately with appropriate therapy instituted, and the use of ORENCIA should be permanently discontinued.

Infections

Serious infections, including sepsis and pneumonia, have been reported in patients receiving ORENCIA. Some of these infections have been fatal. Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy which in addition to their underlying disease, could further predispose them to infections.

Treatment with ORENCIA should not be initiated in patients with active systemic or localized infections. Treatment with ORENCIA also should not be initiated in patients with chronic or latent 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. Physicians should exercise caution when considering the use of ORENCIA in patients with a history of recurrent infection or underlying conditions which may predispose them to infections, such as immunodeficiency disorders, or who have resided in regions where tuberculosis and histoplasmosis are endemic (see [8 ADVERSE REACTIONS](#)).

Prior to treating patients with therapies that modulate the immune system, including ORENCIA, it is appropriate to screen patients for tuberculosis. Should a patient test positive for tuberculosis screening, the patient should be treated in accordance with standard medical practice prior to therapy with ORENCIA.

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

In clinical trials in adult RA patients, the incidence of infections did not appear to increase in the open-label period compared to the double-blind period (see [8 ADVERSE REACTIONS](#)).

During the pediatric clinical trial, there were two cases of varicella and three cases of herpes simplex. All cases resolved appropriately without sequelae.

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

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

Monitor patients for EBV reactivation in accordance with institutional practices. Provide prophylaxis for EBV infection for 6 months post-transplantation to prevent EBV-associated PTLD (see [4.2 Recommended Dose and Dosage Adjustment](#)).

Cytomegalovirus (CMV) invasive disease occurred in patients who received ORENCIA for aGVHD prophylaxis during unrelated HSCT. Of 116 patients who received ORENCIA, 6.9% experienced CMV invasive diseases up to day 225 post-transplant. All the patients who experienced CMV invasive disease were CMV serology positive at baseline. The median time to onset of the event was 91 days post-transplant. CMV invasive diseases predominantly involved the gastrointestinal tract (see [8 ADVERSE REACTIONS](#)).

Monitor patients for CMV infection/reactivation for 6 months post-transplant regardless of the results of donor and recipient pre-transplant CMV serology. Consider prophylaxis for CMV infection/reactivation (see [4.2 Recommended Dose and Dosage Adjustment](#)).

Immunizations

Live vaccines should not be given concurrently with ORENCIA or within 3 months of discontinuation. It is possible that ORENCIA may blunt the effectiveness of some immunizations. No data are available on the secondary transmission of infections by live vaccines to patients receiving ORENCIA.

Patients treated with ORENCIA may receive concurrent non-live vaccines.

Responses to pneumococcal and inactivated influenza vaccines have been studied in subjects receiving ORENCIA. Pneumococcal vaccination with the standard 23-valent vaccine was studied in healthy subjects to assess the effect of ORENCIA on the antibody response to pneumococcal vaccine. This study suggested that ORENCIA may blunt the effectiveness of the immune response but did not significantly inhibit the ability of healthy subjects to develop a clinically significant or positive immune response (at least a 2-fold increase above baseline) to 23-valent pneumococcal vaccines. ORENCIA was evaluated in an open-label study in RA patients administered the 23-valent pneumococcal vaccine. After pneumococcal vaccination, 34 of 46 ORENCIA-treated patients without protective antibody levels at baseline were able to mount an adequate immune response of at least a 2-fold increase in antibody titers to pneumococcal polysaccharide vaccine.

ORENCIA was also evaluated in an open-label study in rheumatoid arthritis patients administered the seasonal inactivated influenza trivalent virus vaccine. After influenza vaccination, 73 of 119 ORENCIA-treated patients without protective antibody levels at baseline were able to mount an adequate immune response of at least a 4-fold increase in antibody titers to trivalent influenza vaccine.

It is recommended that JIA/JRA patients be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating ORENCIA therapy.

Renal

ORENCIA has not been studied in these patient populations. No dose recommendations can be made (see [10.3 Pharmacokinetics](#)).

Respiratory

Use in Patients with Chronic Obstructive Pulmonary Disease (COPD)

Adult COPD patients treated with ORENCIA developed adverse events more frequently than those treated with placebo, including COPD exacerbations, cough, rhonchi, and dyspnea. Use of ORENCIA in patients with rheumatoid arthritis and COPD should be undertaken with caution and such patients should be monitored for worsening of their respiratory status (see [8 ADVERSE REACTIONS](#)).

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies in pregnant women. ORENCIA should not be administered to pregnant women unless the benefits outweigh the potential risks. Reproductive studies have been conducted with abatacept in mice, rats, and rabbits. Abatacept was shown to cross the placenta. (see [16 NON-CLINICAL TOXICOLOGY](#)).

Abatacept may cross the placenta into the serum of infants born to women treated with abatacept during pregnancy. Consequently, these infants may be at increased risk for infection. The safety of administering live vaccines to infants exposed to abatacept in utero is unknown. Administration of live vaccines to infants exposed to abatacept in utero is not recommended for 10 weeks following the mother's last exposure to abatacept during pregnancy.

7.1.2 Breast-feeding

It is not known whether abatacept is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ORENCIA, a decision has to be made on whether to discontinue nursing or to discontinue the medication, taking into account the importance of the medication to the mother.

7.1.3 Pediatrics (6 years of age and older)

Acute Graft Versus Host Disease Prophylaxis

The results of population PK analysis show that weight but not age impact apparent clearance of abatacept (see [4 DOSAGE AND ADMINISTRATION](#)).

No data for children <6 years of age are available to Health Canada, therefore, Health Canada has not authorized an indication for pediatric use <6 years.

The long-term effects of ORENCIA therapy on skeletal, behavioral, cognitive, sexual and immune maturation and development in children are unknown.

No data for the SC injection in children are available to Health Canada; therefore, Health Canada has not authorized an indication for SC pediatric use.

7.1.4 Geriatrics

Rheumatoid Arthritis

A total of 404 patients 65 years of age or older, including 67 patients 75 years and older received ORENCIA in placebo-controlled clinical trials. Similar efficacy was observed in these patients and younger patients. The frequency of serious infection and malignancy among ORENCIA-treated patients over age 65 was

higher than for those under age 65. As there is a higher incidence of infections and malignancies in the elderly population in general, caution should be used when treating the elderly.

Acute Graft Versus Host Disease Prophylaxis

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

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adult RA Patients Treated with Intravenous ORENCIA:

In patients with adult RA, in double-blind and open-label clinical trials, the most serious adverse reactions were serious infections and malignancies (see [8 ADVERSE REACTIONS](#)).

The most commonly reported adverse events (occurring in $\geq 10\%$ of adult RA patients treated with ORENCIA (abatacept) during double-blind placebo-controlled trials were headache, upper respiratory tract infection, nasopharyngitis, and nausea.

JIA/JRA Patients Treated with Intravenous ORENCIA:

Overall frequency of adverse events in the 4-month, lead-in, open-label period was 70.0%; infections occurred at a frequency of 35.8% (see [14 CLINICAL TRIALS](#)). The most common infections were upper respiratory tract infection and nasopharyngitis. The types of infections reported in JIA/JRA patients were generally mild or moderate, resolved without sequelae, and were consistent with those commonly seen in outpatient pediatric and adolescent populations. Other events that occurred at a prevalence of at least 5% were headache, nausea, diarrhea, cough, pyrexia, and abdominal pain.

A total of 6 serious adverse events (acute lymphocytic leukemia, ovarian cyst, varicella infection, disease flare [2], and joint wear) were reported in 190 JIA/JRA patients aged 6 to 17 years treated during the 4-month, lead-in, open-label period.

For the 122 patients who responded in the lead-in period and entered the placebo-controlled, 6-month, withdrawal phase, there were no serious adverse events in 60 ORENCIA-treated patients and 3 serious adverse events in 2 of the 62 placebo-treated patients (hematoma in one patient, varicella and encephalitis in the other).

Upon continued treatment in the open-label extension period, the types of adverse events were consistent with those observed in the double-blind phase, and 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. The majority of the adverse events were mild or moderate in intensity.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adult RA Patients Treated with Intravenous Orenzia:

In patients with adult RA treated with ORENCIA during double-blind, placebo-controlled trials of studies AIM, ATTAIN, ASSURE, IM101100, IM101101, the adverse events most frequently resulting in clinical intervention (interruption or discontinuation of ORENCIA) were due to infection. The most frequently reported infections resulting in dose interruption were upper respiratory tract infection (1.0%), bronchitis (0.7%), and herpes zoster (0.7%). The most frequent infections resulting in discontinuation were pneumonia (0.2%), localized infection (0.2%), and bronchitis (0.1%).

The AGREE (IM101023) study was an active-controlled clinical trial in MTX-naïve adult RA patients treated with intravenous ORENCIA. Subjects were randomized to receive abatacept or placebo for the first 12 months of treatment. In addition, both groups received MTX (see [14 CLINICAL TRIALS](#)). The adverse reaction profile observed in patients receiving ORENCIA plus MTX was generally comparable to that in patients receiving MTX alone except for the acute infusion-related events (See Infusion related reactions). Among MTX-naïve patients treated in AGREE, deaths occurred in 2 (0.8%) subjects in the Orenzia plus MTX group and 4 (1.6%) subjects in the Placebo plus MTX group.

The data described herein reflect exposure to ORENCIA in patients with active RA in placebo-controlled studies (2653 patients with ORENCIA, 1485 with placebo). A subset of these patients received concomitant biologic RA therapy, such as a TNF blocking agent (185 patients with ORENCIA, 84 with placebo).

Table 4 below lists the adverse drug reactions (ADRs - adverse events at least possibly causally-related to treatment) occurring in $\geq 1\%$ of patients treated with ORENCIA during placebo-controlled double-blind rheumatoid arthritis studies.

Table 4: Adverse Drug Reactions (ADRs) Occurring in $\geq 1\%$ of Patients Treated with ORENCIA During Placebo-Controlled Double-Blind Rheumatoid Arthritis Studies*

	ORENCIA^c n = 2653^a (%)	Placebo^c n = 1485^b (%)
Gastrointestinal Disorders		
Nausea	6.0	5.3
Diarrhea	3.2	2.8
Dyspepsia	1.2	0.8
Abdominal Pain	1.0	0.7
Vomiting	1.3	1.2
Mouth Ulceration	1.1	0.5
General Disorders and Administration Site Conditions		
Fatigue	2.8	2.5
Asthenia	1.3	1.1
Pyrexia	1.2	1.3

Local injection site reactions	5.2 ^d	0.8 ^d
Infections and Infestations		
Upper respiratory tract infection	4.4	4.1
Nasopharyngitis	3.3	2.2
Sinusitis	2.4	2.2
Bronchitis	2.7	2.0
Urinary tract infection	2.3	2.0
Influenza	1.5	1.7
Pharyngitis	1.2	1.0
Oral Herpes	1.0	0.5
Herpes Zoster	0.9	0.9
Investigations		
Blood Pressure Increased	1.2	0.3
Musculoskeletal, Connective Tissues and Bone Disorders		
Myalgia	0.8	0.9
Nervous System Disorders		
Headache	8.3	5.8
Dizziness	3.8	3.2
Somnolence	1.6	1.5
Respiratory, Thoracic and Mediastinal Disorders		
Cough	2.1	1.0
Skin and Subcutaneous Tissue Disorders		
Rash	1.7	1.7
Vascular Disorders		
Hypertension	1.9	1.2

^a Includes 185 patients on concomitant biologic RA agents (adalimumab, anakinra, etanercept, or infliximab).

^b Includes 84 patients on concomitant biologic RA agents (adalimumab, anakinra, etanercept, or infliximab).

^c All patients were on concomitant DMARDs.

^d SC administration only. Abatacept (n=286) and placebo (n=133)

* AIM, ATTAIN, ASSURE, IM101101, IM101100, AGREE, IM101043, IM101063, and IM101226

Table 5 below lists the adverse drug reactions (ADRs - adverse events at least possibly causally-related to treatment) occurring in ≥1% of patients treated with ORENCIA + MTX in AGREE (IM101023).

Table 5: Adverse Drug Reactions (ADRs) Occurring in $\geq 1\%$ of Patients in the ORENCIA + MTX in AGREE (IM101023)

Related Adverse Event (Preferred Term)	ORENCIA + MTX n = 256 %	Placebo + MTX n = 253 %
Infections and Infestations		
Bronchitis	3.9	1.2
Nasopharyngitis	3.1	2.0
Urinary tract infection	2.3	2.8
Upper respiratory tract infection	2.3	2.4
Oral herpes	2.0	1.2
Pharyngitis	2.0	0.4
Influenza	1.6	2.8
Herpes zoster	1.2	1.2
Gastrointestinal disorders		
Nausea	4.3	4.3
Mouth ulceration	1.6	0.4
Diarrhoea	1.2	2.4
Nervous system disorders		
Headache	3.5	3.6
Dizziness	3.5	2.4
Investigations		
Alanine aminotransferase increased	3.1	2.4
Aspartate aminotransferase increased	2.0	1.6
Weight increased	1.2	0
Respiratory, thoracic and mediastinal disorders		
Cough	2.7	1.6
General disorders and administration site conditions		
Fatigue	1.2	1.2
Vascular disorders		
Hypertension	1.2	1.6

Infections

In placebo-controlled trials, infections were reported in 22.7% of ORENCIA treated patients and 20.5% of placebo patients. Serious infections were reported in 1.5% of patients treated with ORENCIA and 1.1%

of patients treated with placebo.

Serious infections reported ($\geq 0.2\%$) with ORENCIA versus placebo were pneumonia (0.4% vs. 0.5%) (see [7 WARNINGS AND PRECAUTIONS](#)).

Other infections reported with a higher frequency ($>0.5\%$) with ORENCIA compared to placebo, were rhinitis (2.4% vs. 1.3%), herpes zoster (1.5% vs. 1.4%) bronchitis (6.5% vs. 5.8%), conjunctivitis (2.1% vs. 1.5%), ear infection (1.2% v. 0.6%), fungal skin infection (1.1% vs 0.9%), gastroenteritis viral (0.9% vs. 0.5%), laryngitis (0.9% vs. 0.8%) lower respiratory tract infection (0.8% vs. 0.7%), nasopharyngitis (11.8% vs. 10.0%), onychomycosis (1.0% vs. 0.5%), oral herpes (1.8% vs. 1.3%), pharyngitis (3.5% vs. 3.3%), sinusitis (6.0% vs. 5.9%) tooth abscess (1.5% vs. 1.3%), viral infection (0.8% vs. 0.7%) and pneumonia (1.8% vs. 1.1%).

In controlled clinical studies of 2653 ORENCIA patients and 1485 placebo patients there were two reported cases of tuberculosis, one each in the ORENCIA and placebo groups. These cases were not confirmed by smear, stain or culture.

During continued extensions of open-label clinical trials (AIM, ATTAIN, ASSURE, IM101100, IM101101) in adult RA patients (combined double-blind and open-label mean exposure 22.7-38.8 months), the incidence of infections did not appear to increase compared to the double-blind period (see [7 WARNINGS AND PRECAUTIONS](#)).

In post-marketing experience, opportunistic infections (including herpes zoster and *Pneumocystis jirovecii* pneumonia), have been reported in patients receiving ORENCIA alone or in combination with immunosuppressive agents.

Malignancies

In placebo-controlled clinical trials (2357 patient-years), the frequency of malignancies was similar in ORENCIA and placebo treated patients (1.2% and 0.9%, respectively). In the cumulative period in 7044 patients treated with ORENCIA during 21,011 patient-years, the incidence rate of malignancy was 1.2 per 100 patient-years, and the annualized incidence rate remained stable.

The most frequently reported malignancy in the placebo-controlled clinical trials was non-melanoma skin cancer; 0.6 per 100 patient-years for abatacept-treated patients, 0.4 per 100 patient-years for placebo-treated patients, and 0.5 per 100 patient-years in the cumulative period.

The most frequently reported solid organ cancer in the placebo-controlled clinical trials was lung cancer 0.17 per 100 patient-years for abatacept-treated patients, 0 for placebo-treated patients, and 0.12 per 100 patient-years in the cumulative period. The most common hematologic malignancy was lymphoma 0.04 per 100 patient-years for abatacept-treated patients, 0 for placebo-treated patients, and 0.06 per 100 patient-years in the cumulative period.

Compared with the general population based on the U.S. Surveillance, Epidemiology, and End Results Database, patients with rheumatoid arthritis are at a higher risk for the development of lymphoma. The impact of ORENCIA on malignancies in humans is unknown.

During continued extensions of open-label clinical trials (AIM, ATTAIN, ASSURE, IM101100, IM101101) in adult RA patients (combined double-blind and open-label mean exposure 22.7-38.8 months), the incidence of malignant neoplasms did not appear to increase compared to the double-blind period (see

7 WARNINGS AND PRECAUTIONS).

Infusion-related Reactions

In the clinical studies with ORENCIA, pre-medication to prevent hypersensitivity was not required. Acute infusion-related events (reported within 1 hour of the start of the infusion) in the phase III studies (Studies AIM, ATTAIN, ASSURE, AGREE, IM101101, IM101100 and IM101043 were more common in the ORENCIA-treated patients than the placebo patients (5.2% vs. 3.7%, respectively). The most frequently reported event (>1.0%) with ORENCIA vs. placebo was dizziness (1.5% vs. 1.0%). In the AGREE trial, acute infusion-related events were also more common in the ORENCIA-treated patients than the placebo patients (6.3% in ABA+MTX vs 2% placebo+MTX).

Acute infusion-related events that were reported in >0.1% and ≤ 1% of patients treated with ORENCIA included cardiopulmonary symptoms such as hypotension, blood pressure decrease, tachycardia, bronchospasm, and dyspnea; other symptoms included myalgia, nausea, erythema, flushing, urticaria, hypersensitivity, pruritus, throat tightness, chest discomfort, chills, infusion site extravasation, infusion site pain, infusion site swelling, infusion related reaction, and rash. Most of these reactions were mild to moderate.

In patients treated with ORENCIA in controlled and open-label clinical trials, the events of hypersensitivity, anaphylaxis, and drug hypersensitivity were rarely reported. Other events potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, that occurred within 24 hours of ORENCIA infusion, were uncommon (See [7 WARNINGS AND PRECAUTIONS](#)).

A small proportion of patients in both the ORENCIA and placebo groups discontinued due to an acute infusion-related event (0.3 for ORENCIA, 0.1% for placebo).

Autoantibodies

In controlled trials (AIM, ATTAIN, ASSURE, IM101100, IM101101), 9.7% of ORENCIA treated patients and 10.8% of placebo patients that had negative antinuclear antibody titers at baseline developed positive titers at 12 months. Newly detected anti-dsDNA antibodies were observed in 2.7% of ORENCIA treated patients and 4.7% of placebo patients.

Adverse Reactions in Adult Patients with COPD

In the ASSURE study, there were 37 patients with chronic obstructive pulmonary disease (COPD) who were treated with ORENCIA and 17 COPD patients who were treated with placebo. The COPD patients treated with ORENCIA developed adverse events more frequently than those treated with placebo (97% vs 88%, respectively). Respiratory disorders occurred more frequently in ORENCIA-treated patients compared to placebo-treated patients (43% vs 24%, respectively) including COPD exacerbation, cough, rhonchi, and dyspnea. A greater percentage of ORENCIA-treated patients developed a serious adverse event compared to placebo-treated patients (27% vs 6%), including COPD exacerbation (3 of 37 patients [8%]) and pneumonia (1 of 37 patients [3%]).

Adult RA Patients Treated with Subcutaneous ORENCIA:

Study IM101-174 was a large (n=1457) 6-month controlled, non-inferiority study that compared the efficacy and safety of abatacept administered subcutaneously (SC) and intravenously (IV) in patients with rheumatoid arthritis, receiving background methotrexate, and experiencing an inadequate response to

MTX (MTXIR) (see 14 CLINICAL TRIALS). Patients were stratified by body weight (<60kg, 60 to 100 kg and >100kg) and randomized in a double-blind manner 1:1 to either SC abatacept 125 mg weekly with an IV abatacept loading dose at Day 1 or abatacept IV infusion on Days 1, 15, 29, and then every 28.

Table 6: Adverse Drug Reactions (ADRs) Occurring in \geq 1% of Patients in subcutaneous ORENCIA (IM101174)*

Related Adverse Event (Preferred Term)	SC ORENCIA n = 736 %	IV ORENCIA n = 721 %
Infections and Infestations	11.3	12.3
Upper respiratory tract infection	2.0	1.8
Bronchitis	1.6	2.1
Nasopharyngitis	1.2	1.4
Sinusitis	1.2	0.3
Gastrointestinal Disorders	4.8	5.8
Nausea	1.6	1.5
Diarrhoea	1.1	2.2
Nervous System Disorders	4.6	5.3
Headache	2.2	4.0
Somnolence	1.8	0.4

*All patients received an IV loading dose (by weight) on Day 1.

Due to the SC route of administration, injection site reactions were evaluated and are discussed in the sections below.

Injection Site Reactions in Adult RA Patients Treated with SC ORENCIA

The overall frequency of injection site reactions was 2.6% (19/736) and 2.5% (18/721) for the subcutaneous abatacept group and intravenous abatacept group (SC placebo), respectively. All injection site reactions were described as mild to moderate (hematoma, pruritus, or erythema) and generally did not necessitate drug discontinuation. Moderate injection site reactions were reported in 1/736 patients in the SC group vs. 3/721 patients in the IV group.

Adult PsA Patients Treated with ORENCIA:

The safety of ORENCIA was evaluated in 594 patients with psoriatic arthritis (PsA) (341 patients on ORENCIA and 253 patients on placebo), in two randomized, double-blind, placebo-controlled trials. Of the 341 patients who received ORENCIA, 213 patients received subcutaneous ORENCIA (IM101332) and 128 patients received intravenous ORENCIA (IM101158). In PsA-I (IM101332), during the 24-week placebo-controlled period, the overall proportion of patients with adverse reactions (adverse events at least possibly causally-related to treatment) was similar in the ORENCIA and placebo treatment groups (15.5% and 11.4%, respectively). In PsA-I, there were no adverse reactions that occurred at \geq 1% in the ORENCIA treatment group during the 24-week placebo-controlled period.

The safety profile was comparable between studies PsA-I and PsA-II and consistent with the safety profile in rheumatoid arthritis.

Adult and Pediatric Patients undergoing unrelated donor hematopoietic stem cell transplantation (HSCT) for Prophylaxis of Acute Graft versus Host Disease

The data described herein were from the GVHD-1 clinical study with ORENCIA at a dose of 10 mg/kg for aGVHD prophylaxis in patients 6 years and older with hematologic malignancies who were undergoing unrelated HSCT wherein all patients were receiving calcineurin inhibitor and methotrexate as the standard of care for aGVHD prophylaxis.

In GVHD-1, two cohorts were studied: 1) A single-arm cohort of ORENCIA-treated patients (n=43) who underwent 7 of 8 Human leukocyte antigen (HLA)-matched HSCT from unrelated donors (7 of 8 cohort) and 2) A randomized cohort comprised of ORENCIA-treated patients (n=73) and placebo-treated patients (n=69) who underwent 8 of 8 HLA-matched HSCT from unrelated donors (8 of 8 cohort). Of the 116 patients who received ORENCIA, 30 (26%) were 6 to 17 years of age (see [14 CLINICAL TRIALS](#)).

The safety information from the date of first dose of ORENCIA up to Day 225 post-transplantation from the GVHD-1 study is presented below. The incidence of adverse reactions was determined based on pooled data of ORENCIA-treated patients from the 2 study cohorts (n=116).

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

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

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

The common (≥1%) adverse reactions in ORENCIA-treated patients and at least 2% greater than placebo are summarized in Table 7.

Table 7: Adverse Reactions (≥1%) in patients with aGVHD who received ORENCIA with >2% difference (ORENCIA vs. Placebo) in study GVHD-1

Adverse Reaction	7 of 8 Cohort		8 of 8 Cohort			
	ORENCIA (+CNI and MTX) (N=43)		ORENCIA (+CNI and MTX) (N=73)		Placebo (+CNI and MTX) (N=69)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
TOTAL SUBJECTS WITH AN EVENT	43 (100.0)	43 (100.0)	73 (100.0)	73 (100.0)	69 (100.0)	69 (100.0)
Blood and lymphatic system disorders	38 (88.4)	38 (88.4)	61 (83.6)	61 (83.6)	63 (91.3)	62 (89.9)

Anaemia	24 (55.8)	24 (55.8)	50 (68.5)	50 (68.5)	39 (56.5)	39 (56.5)
Gastrointestinal disorders	31 (72.1)	31 (72.1)	62 (84.9)	62 (84.9)	61 (88.4)	61 (88.4)
Mouth haemorrhage	4 (9.3)	4 (9.3)	2 (2.7)	2 (2.7)	3 (4.3)	3 (4.3)
General disorders and administration site conditions	16 (37.2)	8 (18.6)	23 (31.5)	15 (20.5)	23 (33.3)	13 (18.8)
Pyrexia	12 (27.9)	4 (9.3)	14 (19.2)	6 (8.2)	14 (20.3)	3 (4.3)
Immune system disorders	19 (44.2)	16 (37.2)	25 (34.2)	23 (31.5)	24 (34.8)	23 (33.3)
Graft versus host disease in gastrointestinal tract	9 (20.9)	5 (11.6)	19 (26.0)	15 (20.5)	13 (18.8)	13 (18.8)
Graft versus host disease in skin	8 (18.6)	8 (18.6)	5 (6.8)	5 (6.8)	9 (13.0)	8 (11.6)
Acute graft versus host disease in skin	4 (9.3)	4 (9.3)	5 (6.8)	4 (5.5)	3 (4.3)	3 (4.3)
Chronic graft versus host disease in eye	3 (7.0)	1 (2.3)	0	0	1 (1.4)	1 (1.4)
Infections and infestations	30 (69.8)	30 (69.8)	50 (68.5)	50 (68.5)	53 (76.8)	52 (75.4)
Cytomegalovirus infection reactivation	8 (18.6)	8 (18.6)	15 (20.5)	15 (20.5)	9 (13.0)	9 (13.0)
Pneumonia	8 (18.6)	8 (18.6)	9 (12.3)	9 (12.3)	7 (10.1)	6 (8.7)
Cytomegalovirus infection	3 (7.0)	3 (7.0)	8 (11.0)	8 (11.0)	6 (8.7)	6 (8.7)
Urinary tract infection	5 (11.6)	5 (11.6)	5 (6.8)	4 (5.5)	6 (8.7)	6 (8.7)
Upper respiratory tract infection	1 (2.3)	0	8 (11.0)	6 (8.2)	4 (5.8)	3 (4.3)
Epstein-Barr virus infection reactivation	3 (7.0)	3 (7.0)	1 (1.4)	1 (1.4)	1 (1.4)	1 (1.4)
Mucosal infection	2 (4.7)	2 (4.7)	1 (1.4)	1 (1.4)	1 (1.4)	1 (1.4)
Investigations	43 (100.0)	43 (100.0)	68 (93.2)	68 (93.2)	69 (100.0)	69 (100.0)
CD4 lymphocytes decreased	6 (14.0)	6 (14.0)	10 (13.7)	10 (13.7)	6 (8.7)	6 (8.7)
Aspartate aminotransferase increased	8 (18.6)	8 (18.6)	7 (9.6)	7 (9.6)	11 (15.9)	11 (15.9)

Urine output decreased	1 (2.3)	1 (2.3)	4 (5.5)	4 (5.5)	1 (1.4)	1 (1.4)
Activated partial thromboplastin time prolonged	0	0	4 (5.5)	4 (5.5)	1 (1.4)	1 (1.4)
Metabolism and nutrition disorders	31 (72.1)	31 (72.1)	66 (90.4)	66 (90.4)	65 (94.2)	65 (94.2)
Dehydration	9 (20.9)	9 (20.9)	36 (49.3)	36 (49.3)	30 (43.5)	30 (43.5)
Decreased appetite	17 (39.5)	17 (39.5)	21 (28.8)	21 (28.8)	25 (36.2)	25 (36.2)
Hyperglycaemia	11 (25.6)	11 (25.6)	15 (20.5)	15 (20.5)	16 (23.2)	16 (23.2)
Hyponatraemia	6 (14.0)	6 (14.0)	11 (15.1)	11 (15.1)	9 (13.0)	9 (13.0)
Hypermagnesaemia	2 (4.7)	2 (4.7)	13 (17.8)	13 (17.8)	7 (10.1)	7 (10.1)
Acidosis	1 (2.3)	1 (2.3)	5 (6.8)	5 (6.8)	1 (1.4)	1 (1.4)
Musculoskeletal and connective tissue disorders	8 (18.6)	7 (16.3)	22 (30.1)	22 (30.1)	11 (15.9)	11 (15.9)
Back pain	3 (7.0)	3 (7.0)	7 (9.6)	7 (9.6)	2 (2.9)	2 (2.9)
Muscular weakness	0	0	6 (8.2)	6 (8.2)	2 (2.9)	2 (2.9)
Pain in extremity	3 (7.0)	3 (7.0)	3 (4.1)	3 (4.1)	2 (2.9)	2 (2.9)
Myalgia	0	0	3 (4.1)	3 (4.1)	1 (1.4)	1 (1.4)
Nervous system disorders	7 (16.3)	7 (16.3)	17 (23.3)	15 (20.5)	15 (21.7)	13 (18.8)
Peripheral sensory neuropathy	1 (2.3)	1 (2.3)	6 (8.2)	6 (8.2)	1 (1.4)	1 (1.4)
Posterior reversible encephalopathy syndrome	1 (2.3)	1 (2.3)	3 (4.1)	3 (4.1)	1 (1.4)	1 (1.4)
Psychiatric disorders	3 (7.0)	3 (7.0)	11 (15.1)	11 (15.1)	9 (13.0)	9 (13.0)
Delirium	2 (4.7)	2 (4.7)	5 (6.8)	5 (6.8)	3 (4.3)	3 (4.3)
Anxiety	1 (2.3)	1 (2.3)	4 (5.5)	4 (5.5)	2 (2.9)	2 (2.9)
Renal and urinary disorders	8 (18.6)	8 (18.6)	18 (24.7)	18 (24.7)	15 (21.7)	15 (21.7)
Acute kidney injury	4 (9.3)	3 (7.0)	11 (15.1)	11 (15.1)	7 (10.1)	7 (10.1)
Chronic kidney disease	3 (7.0)	3 (7.0)	8 (11.0)	8 (11.0)	4 (5.8)	4 (5.8)
Haematuria	3 (7.0)	3 (7.0)	2 (2.7)	2 (2.7)	2 (2.9)	2 (2.9)
Respiratory, thoracic	17 (39.5)	16 (37.2)	23 (31.5)	23 (31.5)	30 (43.5)	30 (43.5)

and mediastinal disorders						
Epistaxis	5 (11.6)	5 (11.6)	12 (16.4)	12 (16.4)	7 (10.1)	7 (10.1)
Hypoxia	8 (18.6)	7 (16.3)	7 (9.6)	7 (9.6)	9 (13.0)	9 (13.0)
Pneumonitis	2 (4.7)	2 (4.7)	1 (1.4)	1 (1.4)	1 (1.4)	1 (1.4)
Vascular disorders	27 (62.8)	27 (62.8)	38 (52.1)	38 (52.1)	36 (52.2)	36 (52.2)
Hypertension	21 (48.8)	21 (48.8)	31 (42.5)	31 (42.5)	26 (37.7)	26 (37.7)

Infections

The incidence of overall grade 3 or higher infections was 69% in ORENCIA-treated patients and 75% in placebo group. The most frequently reported viral infections were CMV viremia and EBV viremia. CMV viremia was reported in 47.4% of patients treated with ORENCIA and 43.5% of patients treated with placebo; CMV invasive disease was reported in 6.9% of patients treated with ORENCIA and 2.9% of patients treated with placebo. EBV viremia was reported in 39.7% of patients treated with ORENCIA and 30.4% of patients treated with placebo (see [7 WARNINGS AND PRECAUTIONS](#)).

Infusion-related Reactions

Peri-infusional adverse events within 24 hours of infusion were reported in 12.1% of patients treated with ORENCIA, similar to the placebo rate. The most frequent reactions were nausea (6.9%) and infusion-related reaction (2.6%).

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

JIA/JRA Patients Treated with Intravenous ORENCIA:

In general, the adverse events in pediatric and adolescent patients were similar in frequency and type to those seen in adult patients, and the majority of the adverse events were mild or moderate in intensity (see [7 WARNINGS AND PRECAUTIONS](#) and [8.2 Clinical Trial Adverse Drug Reactions](#)).

Error! Reference source not found. below lists the adverse drug reactions (ADRs - adverse events at least possibly causally-related to treatment) occurring in $\geq 1\%$ of pediatric patients receiving ORENCIA in period A (open label, abatacept lead-in portion) of the three part study conducted in children with polyarticular JIA.

Table 8: Adverse Drug Reactions (ADRs) Occurring in $\geq 1\%$ of Patients Treated with ORENCIA During Period A (Open label, abatacept lead-in portion) of the Juvenile Idiopathic Arthritis Study

Related Adverse Event (Preferred Term)	ORENCIA n = 190 %
Blood and Lymphatic System Disorders	
Leukopenia	1.6
Gastrointestinal Disorders	
Nausea	2.1
Abdominal Pain	1.1

Aphthous stomatitis	1.1
Diarrhea	1.1
Mouth ulceration	1.1
Vomiting	1.1
General Disorders and Administration Site Conditions	
Asthenia	1.1
Fatigue	1.1
Pyrexia	1.1
Infections and Infestations	
Sinusitis	2.1
Upper respiratory tract infection	1.6
Nasopharyngitis	1.1
Acute otitis media	1.1
Rhinitis	1.1
Nervous System Disorders	
Headache	5.3
Dizziness	2.6
Renal and Urinary Disorders	
Hematuria	1.1
Skin and Subcutaneous Tissue Disorders	
Pruritus	1.1
Rash	1.1
Vascular Disorders	
Flushing	1.1

Error! Reference source not found. below lists the adverse drug reactions (ADRs - adverse events at least possibly causally-related to treatment) occurring in $\geq 1\%$ of pediatric patients receiving ORENCIA in period B (double-blind phase) of the three-part study conducted in children with polyarticular JIA.

Table 9: Adverse Drug Reactions (ADRs) Occurring in $\geq 1\%$ of Patients Treated with ORENCIA During Period B (Double-blind, placebo-controlled portion) of the Juvenile Idiopathic Arthritis Study

Related Adverse Event (Preferred Term)	ORENCIA n = 60 %	Placebo n = 62 %
Blood and Lymphatic System Disorders		
Leukopenia	0	3.2

Eosinophilia	0	1.6
Neutropenia	0	1.6
Gastrointestinal Disorders		
Abdominal Pain	1.7	1.6
Nausea	1.7	1.6
Aphthous stomatitis	1.7	0
Gingival hyperplasia	0	1.6
General Disorders and Administration Site Conditions		
Pyrexia	0	1.6
Infections and Infestations		
Sinusitis	1.7	3.2
Influenza	1.7	1.6
Rhinitis	1.7	1.6
Tinea versicolor	1.7	1.6
Upper respiratory tract infection	1.7	1.6
Bacteriuria	1.7	0
Otitis externa	1.7	0
Acute otitis media	0	1.6
Skin candida	0	1.6
Varicella	0	1.6
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)		
Skin papilloma	0	1.6
Reproductive System and Breast Disorders		
Vaginal discharge	0	1.6
Nervous System Disorders		
Headache	1.7	1.6
Encephalitis	0	1.6
Renal and Urinary Disorders		
Leukocyturia	1.7	0
Skin and Subcutaneous Tissue Disorders		
Pityriasis	1.7	0

Skin lesion	1.7	0
Atopic dermatitis	0	1.6
Eczema	0	1.6
Vascular Disorders		
Hypotension	1.7	0

Error! Reference source not found. below lists the adverse drug reactions (ADRs - adverse events at least possibly causally-related to treatment) occurring in $\geq 1\%$ of pediatric patients receiving ORENCIA in period C (open label extension phase) of the three part study conducted in children with polyarticular JIA.

Table 10: Adverse Drug Reactions (ADRs) Occurring in $\geq 1\%$ of Patients Treated with ORENCIA During Open Label Period (Period C) of the Juvenile Idiopathic Arthritis Study

Related Adverse Event (Preferred Term)	ORENCIA n = 153 %
Blood and Lymphatic System Disorders	
Eosinophilia	3.9
Leukopenia	2.6
Eye Disorders	
Conjunctivitis	1.3
Gastrointestinal Disorders	
Abdominal Pain	2.0
Nausea	2.0
Vomiting	1.3
General Disorders and Administration Site Conditions	
Infusion related reaction	1.3
Infections and Infestations	
Upper respiratory tract infection	5.9
Sinusitis	3.3
Rhinitis	2.0
Bacteriuria	1.3
Herpes simplex	1.3
Otitis media	1.3
Tonsillitis	1.3
Vulvovaginitis	1.3

Nervous System Disorders	
Dizziness	1.3
Renal and Urinary Disorders	
Hematuria	1.3
Respiratory, Thoracic and Mediastinal Disorders	
Cough	2.6
Pharyngolaryngeal Pain	1.3
Skin and Subcutaneous Tissue Disorders	
Skin lesion	1.3
Urticaria	1.3

Infections

Adverse events of infections were reported in 36% of patients in the 4-month, lead-in, open-label period. The most common infections were upper respiratory tract infections [14 (7.4%)] and nasopharyngitis [11 (5.8%)]. Other than upper respiratory tract infections and nasopharyngitis, few infectious adverse events were reported. No pneumonias or opportunistic infections were observed.

During the double-blind phase, adverse events of infections were reported in the abatacept and placebo groups [45% and 44%]; influenza 5 [8.3%] vs 4 [6.5%], bacteriuria 4 [6.7%] vs 0 [0%], nasopharyngitis 4 [6.7%] vs 3 [4.8%], and upper respiratory tract infections 4 [6.7%] vs 5 [8.1%], were the most frequently reported events.

Infusion-related Reactions

In the open-label lead-in phase of the study, eight (4.2%) patients experienced acute infusional adverse events; all but one was mild in intensity and none was serious. Most infusional adverse events were reported as single events in one patient each with no recurrences; headache and dizziness occurred in four and two patients, respectively. During the double-blind phase, acute infusional adverse events were reported in 1.7% and 3.2% of the abatacept and placebo groups, respectively; all were either mild or moderate in intensity and none were serious.

Autoantibodies

In Period A of the pediatric clinical trial, 10.6% of ORENCIA treated patients that had negative antinuclear antibody titers at baseline had positive titers at Day 113. In Period B, 5.9% of ORENCIA treated patients and 4.0% of placebo patients that had negative antinuclear antibody titers at baseline had positive titers at Day 169.

In Period A, newly detected anti-dsDNA antibodies were observed in 6.2% of ORENCIA treated patients at Day 113. In Period B, newly detected anti-dsDNA antibodies were observed in 2.3% of ORENCIA treated patients and 0% of placebo patients at Day 169.

Malignancies

A single case of acute lymphocytic leukemia was reported in the pediatric trial. No other malignancies were reported.

Acute Graft Versus Host Disease Prophylaxis

The safety of ORENCIA for the prophylaxis of acute graft versus host disease (aGVHD), in combination with calcineurin inhibitor and methotrexate, in pediatric patients undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated donor was evaluated in Study GVHD-1. The types of adverse events reported in the 6 to 17-year-old population were consistent with those expected in a pediatric patient population with hematologic malignancies undergoing HSCT. Review of those events did not identify any unexpected safety concerns among ORENCIA-treated pediatric patients (see [8.2 Clinical Trial Adverse Drug Reactions](#)).

8.3 Less Common Clinical Trial Adverse Reactions

Adult RA Patients Treated with Intravenous Orencia:

ADRs reported in less than 1% of patients receiving ORENCIA in the double-blind clinical trials (n=2653) and not listed in Table 4 are listed below by body system.

Blood and lymphatic system disorders: leukopenia, neutropenia, thrombocytopenia, thrombocythaemia, bone marrow failure, bone marrow depression, iron deficiency anaemia, lymph node pain, lymphocytosis, monocytopenia, increased tendency to bruise, pancytopenia.

Cardiac disorders: angina pectoris, angina unstable, coronary artery occlusion, palpitations, tachycardia, bradycardia, arrhythmia, atrioventricular block first degree, myocarditis post infection, supraventricular extrasystoles, ventricular extrasystoles.

Ear and labyrinth disorders: ear discomfort, vertigo, deafness bilateral, ear congestion, eustachian tube obstruction, sensation of pressure in ear.

Endocrine disorders: goitre.

Eye disorders: dacryostenosis acquired, diplopia, visual acuity reduced, eye irritation, vision blurred, visual disturbance, eye pruritus, blindness unilateral, conjunctival haemorrhage, conjunctival hyperaemia, corneal ulcer, eye haemorrhage, eye inflammation, eye pain, eye redness, eye swelling, keratitis, ulcerative keratitis, ocular hyperaemia, presbyopia, photophobia, retinal vein occlusion, retinopathy hypertensive, scotoma.

Gastrointestinal disorders: anal pruritus, aphthous stomatitis, aphthous ulcer, constipation, stomatitis, dental caries, gastritis, loose stools, gingivitis, gastroesophageal reflux disease, aptyalism, abdominal distension, abnormal faeces, diverticulum, epigastric discomfort, oral discomfort, tongue blistering, stomach discomfort, duodenitis, enteritis, faeces discoloured, frequent bowel movements, gastrointestinal disorder, gastroesophagitis, gingival bleeding, gingival discomfort, gingival ulceration, glossodynia, infrequent bowel movements, intestinal haemorrhage, lip dry, lip pain, oesophagitis, odynophagia, oral mucosal blistering, pancreatic mass, pancreatitis, paraesthesia oral, parotid gland enlargement, proctalgia, salivary gland enlargement, salivary hypersecretion, steatorrhoea, upper gastrointestinal haemorrhage, oral mucosal erythema.

General disorders and administration site conditions: axillary pain, influenza like illness, pain, injection site reaction, feeling cold, gait disturbance, injection site bruising, injection site pain, injection site swelling, injection site warmth, nodule, injection site erythema, mucosal inflammation, non-cardiac chest pain, feeling hot, infusion site burning, infusion site erythema, infusion site thrombosis, infusion

site rash, infusion site reaction, local swelling, inflammation localised, infusion related reaction, injection site haemorrhage, application site pain, facial pain, generalised oedema, impaired healing, infusion site inflammation, infusion site pruritus, injection site hypersensitivity, injection site phlebitis, injection site thrombosis, mucosal ulceration, pitting oedema, sluggishness, ulcer, sudden death, vessel puncture site pain.

Hepatobiliary disorders: drug-induced liver injury, hepatic function abnormal, hypertransaminasaemia.

Immune system disorders: rheumatoid nodule, hypersensitivity, drug hypersensitivity, hypogammaglobulinaemia, seasonal allergy.

Infections and Infestations: acarodermatitis, pneumonia, fungal skin infection, bacterial vaginosis, bronchitis acute, ear infection, giardiasis, infected bite, respiratory tract infection, laryngitis, localised infection, lower respiratory tract infection, vaginal mycosis, tooth infection, herpes virus infection, infected skin ulcer, onychomycosis, tracheitis, gingival infection, body tinea, oral fungal infection, paronychia, tonsillitis bacterial, viral tonsillitis, typhoid fever, postoperative infection, pyoderma, pyuria, soft tissue infection, bronchopneumonia, eye infection, eye infection fungal, eye infection viral, genital infection fungal, nail infection, pneumonia bacterial, pulpitis dental, pyelonephritis, pyelonephritis acute, urinary tract infection bacterial, vaginal candidiasis, candidiasis, pharyngotonsillitis, vaginitis, staphylococcal pharyngitis, abscess intestinal, abscess oral, acute sinusitis, arthritis bacterial, bacteraemia, blister infected, borrelia infection, bronchopulmonary aspergillosis, bursitis infective, cellulitis staphylococcal, cervicitis, conjunctivitis, conjunctivitis bacterial, ear lobe infection, empyema, enterobiasis, escherichia urinary tract infection, eyelid infection, gastrointestinal infection, gingival abscess, groin abscess, hepatitis E, herpes simplex, infected bunion, infection, labyrinthitis, laryngopharyngitis, laryngotracheo bronchitis, lobar pneumonia, mycetoma mycotic, oral pustule, papilloma viral infection, peridiverticular abscess, pharyngitis streptococcal, pneumonia haemophilus, pneumonia influenzal, rash pustular, respiratory tract infection bacterial, rhinitis, skin bacterial infection, streptococcal sepsis, superinfection, urosepsis, vaginitis bacterial, varicella, vulvovaginal mycotic infection, wound infection staphylococcal, pneumonia pseudomonal, lower respiratory tract infection bacterial, postoperative wound infection, respiratory tract infection.

Injury, poisoning and procedural complications: fall, excoriation, joint dislocation, compression fracture, injury asphyxiation, joint injury, limb traumatic amputation, neck injury, ligament sprain, overdose, procedural headache, scar, toxicity to various agents, wound secretion.

Investigations: antinuclear antibody increased, blood pressure decreased, weight increased, hepatic enzyme increased, white blood cell count decreased, liver function test abnormal, heart rate increased, mean cell volume increased, transaminases increased, bacterial culture positive, blood glucose increased, blood immunoglobulin G decreased, blood immunoglobulin M decreased, blood iron decreased, blood phosphorus increased, blood potassium increased, blood potassium decrease, blood sodium decreased, electrocardiogram repolarisation abnormality, haematocrit decreased, heart rate irregular, platelet count decreased, platelet count increased, red blood cell count decreased, respiratory rate increased, white blood cells urine positive, staphylococcus test positive.

Metabolism and nutrition disorders: anorexia, decreased appetite, glucose tolerance impaired, hyperlipidaemia, hyperuricaemia, hypoalbuminaemia, hypocalcaemia, type 2 diabetes mellitus.

Musculoskeletal and connective tissue disorders: pain in extremity, arthralgia, muscle cramp, nodule on extremity, myofascial pain syndrome, night cramps, chest wall pain, joint swelling, lupus-like syndrome, muscle contracture, muscle fatigue, myositis, neck mass, pain in jaw, sensation of heaviness, systemic lupus erythematosus, tendonitis, soft tissue swelling, ligament disorder, limb discomfort.

Neoplasms benign, malignant and unspecified (including cysts and polyps): Bowen's disease, skin papilloma, basal cell carcinoma, fibroadenoma of breast, intraductal papilloma of breast, lung neoplasm malignant, lymphoma, renal cell carcinoma stage unspecified, seborrhoeic keratosis, squamous cell carcinoma of skin.

Nervous System Disorders: paraesthesia, tremor, hypoaesthesia, dyskinesia, restless legs syndrome, syncope vasovagal, facial palsy, reflex sympathetic dystrophy, complex partial seizures, disturbance in attention, formication, head discomfort, hyperaesthesia, loss of consciousness, migraine with aura, neuralgia, neuromyopathy, presyncope, sciatica, sedation, sensory disturbance, syncope, tension headache visual field defect.

Psychiatric disorders: insomnia, depression, anxiety, irritability, nervousness, fear of death, agitation, depressed mood, elevated mood, listless, nightmare, restlessness, screaming, sleep disorder.

Renal and urinary disorders: pollakiuria, proteinuria, urinary incontinence.

Reproductive system and breast disorders: amenorrhoea, menorrhagia, metrorrhagia, genital discharge, breast cyst, breast mass, genital pruritus female, vaginal discharge, breast hyperplasia, erectile dysfunction, menopausal symptoms, oligomenorrhoea, urine haemorrhage, vulvovaginal pruritus.

Respiratory, thoracic and mediastinal disorders: asphyxia, bronchial hyperreactivity, bronchiectasis, dyspnoea, dyspnoea exertional, nasal congestion, throat irritation, productive cough, chronic obstructive pulmonary disease exacerbation, crackles lung, hoarseness, lung crepitation, throat tightness, rales, nasal discomfort, bronchial polyp, chronic obstructive pulmonary disease, dry throat, dyspnoea exacerbated, haemoptysis, nasal disorder, nasal dryness, nasal obstruction, nasal pruritus, nasal ulcer, paranasal sinus discomfort, pharyngolaryngeal pain, pulmonary embolism, pulmonary mass, rhinitis seasonal, sinus pain, upper respiratory tract congestion.

Skin and Subcutaneous Tissue Disorders: alopecia, dyshidrotic eczema, exfoliative rash, guttate psoriasis, hyperhidrosis, erythema, dermatitis, dry skin, ecchymosis, dermatitis allergic, rash macular, acne, dermal cyst, psoriasis, rash maculo-papular, actinic keratosis, erythema multiforme, skin burning sensation, face oedema, leukocytoclastic vasculitis, rash scaly, dermatitis acneiform, dermatitis atopic, dermatitis bullous, dermatitis psoriasiform, dyshidrosis, ephelides, exanthem, localised exfoliation, nail disorder, onychorrhexis, onychoclasia, palmoplantar keratoderma, panniculitis, petechiae, pigmentation disorder, pityriasis, pyoderma, madarosis, nail dystrophy, scar, seborrhoea, skin desquamation, skin discolouration, skin induration, skin nodule, vasculitic rash, scab, skin mass.

Surgical and medical procedures: hormone replacement therapy.

Vascular disorders: flushing hypotension, hot flush, hyperaemia, hypertensive crisis, lymphoedema, blood pressure inadequately controlled, rheumatoid vasculitis, vein pain, capillary fragility, deep vein thrombosis, infarction, peripheral coldness, peripheral ischaemia, varicose ulceration, vascular rupture, vasculitis necrotising.

ADRs reported in less than 1% of patients receiving ORENCIA + MTX in the AGREE Trial and not listed in Table 5 are listed below by body system.

Blood and lymphatic system disorders: anaemia

Ear and labyrinth disorders: vertigo

Eye disorders: eye irritation, presbyopia

Gastrointestinal disorders: vomiting, abdominal pain upper, dry mouth, dyspepsia, abdominal pain, gastritis, gastrointestinal haemorrhage, gastrointestinal pain, gingival ulceration, lip dry

General disorders and administration site conditions: malaise, chest pain, asthenia, chest discomfort, axillary pain, chills, feeling hot, infusion related reaction, infusion site erythema, infusion site pain, sudden death

Hepatobiliary disorders: hepatic function abnormal

Immune system disorders: hypersensitivity

Infections and infestations: gastroenteritis, tooth abscess, pneumonia, respiratory tract infection, sinusitis, tonsillitis, viral upper respiratory tract infection, acariasis, furuncle, genital herpes, tinea pedis, acarodermatitis, bacterial infection, bronchopneumonia, cystitis, ear infection, fungal rash, laryngitis, lung infection pseudomonal, rhinitis, sepsis, soft tissue infection, tinea versicolour, vaginal infection

Injury, poisoning and procedural complications: contusion

Investigations: transaminases increased, gamma-glutamyltransferase increased, blood alkaline phosphatase increased, blood pressure increased

Metabolism and nutrition disorders: diabetes mellitus

Musculoskeletal and connective tissue disorders: back pain, joint swelling, ligament disorder, musculoskeletal stiffness, pain in extremity, systemic lupus erythematosus

Neoplasms benign, malignant and unspecified (including cysts and polyps): lung neoplasm, skin papilloma

Nervous system disorders: dysgeusia, paraesthesia

Psychiatric disorders: depression, insomnia, nervousness

Reproductive system and breast disorders: breast mass, breast pain

Respiratory, thoracic and mediastinal disorders: nasal congestion, pharyngolaryngeal pain, rhinorrhoea, sinus congestion, dyspnoea exertional, nasal discomfort, nasal dryness

Skin and subcutaneous tissue disorders: rash, alopecia, urticaria, acne, eczema, nail dystrophy, pruritus, psoriasis, skin lesion

Vascular disorders: flushing, hyperaemia, hypotension

Adult RA Patients Treated with Subcutaneous ORENCIA:

ADRs reported in less than 1% of patients receiving SC ORENCIA in the IM101-174 Trial and not listed in Table 6 are listed below by body system.

Infection and infestation: urinary tract infection, pharyngitis, gastroenteritis, influenza, herpes zoster, oral herpes, subcutaneous abscess, cystitis, fungal skin infection, lower respiratory tract infection, herpes simplex, tonsillitis, candidiasis, pharyngotonsillitis, viral upper respiratory tract infection, cellulitis, pneumonia, gastroenteritis viral, tooth abscess, varicella, acute tonsillitis, asymptomatic bacteriuria, bronchopneumonia, ear infection, furuncle, infection, laryngitis, pneumonia primary atypical, pyelonephritis, sepsis, staphylococcal sepsis, tinea versicolour, tracheitis, typhoid fever, infected skin ulcer, respiratory tract infection, arthritis infective, body tinea, cervicitis, eye infection, gastrointestinal viral infection, genital herpes, herpes virus infection, infective tenosynovitis, localized infection, oral candidiasis, oral fungal infection, pyelonephritis acute, rash pustular, rhinitis, skin candida, tonsillitis bacterial, vulvovaginal candidiasis

General disorders and administration site conditions: fatigue, oedema peripheral, injection site pruritus, injection site erythema, pyrexia, asthenia, malaise, injection site haematoma, chills, influenza like illness, injection site rash, injection site pain, injection site papule, injection site reaction, chest pain, oedema, chest discomfort, death, injection site haemorrhage, injection site irritation, injection site swelling, injection site vesicles, nodule, thirst, injection site urticaria, administration site reaction, infusion site thrombosis, injection site discolouration, injection site macule, mucosal inflammation, pain

Gastrointestinal disorders: abdominal pain, gastritis, vomiting, mouth ulceration, abdominal pain upper, constipation, aphthous stomatitis, dyspepsia, stomatitis, gingivitis, haematochezia, intra-abdominal haematoma, odynophagia, abdominal discomfort, abdominal pain lower, abnormal faeces, cheilitis, dysphagia, faeces discoloured, flatulence, lip oedema, lip ulceration, plicated tongue, salivary gland enlargement

Nervous system disorders: dizziness, paraesthesia, hypoaesthesia, dysgeusia, hemicephalgia, migraine, muscle contractions involuntary, tremor

Skin and subcutaneous tissue disorders: urticaria, erythema, rash, alopecia, rash papular, skin exfoliation, psoriasis, pruritus, acne, purpura, skin lesion, dermatitis, rash pruritic, drug eruption, eczema, hair disorder, hair growth abnormal, hair texture abnormal, hyperhidrosis, onychoclasia, skin ulcer, vasculitic rash

Respiratory, thoracic and mediastinal disorders: cough, oropharyngeal pain, dyspnoea, sinus congestion, asthmatic crisis, dyspnoea exertional, hypoxia, interstitial lung disease, postnasal drip, rhinorrhoea, lung disorder, nasal congestion, paranasal sinus hypersecretion, pleural effusion

Investigations: alanine aminotransferase increased, blood pressure increased, aspartate aminotransferase increased, liver function test abnormal, blood pressure diastolic increased, DNA antibody positive, heart rate increased, white blood cell count decreased, blood creatinine increased, blood phosphorus decreased, body temperature increased, gamma-glutamyltransferase increased, weight increased

Musculoskeletal and connective tissue disorders: back pain, arthralgia, pain in extremity, myalgia, muscles spasms, bursitis, muscular weakness, osteopenia, muscle tightness, musculoskeletal pain, neck pain, nodule on extremity

Injury, poisoning and procedural complications: drug toxicity, contusion, procedural pain, subcutaneous haematoma, procedural nausea, excoriation, muscle injury, procedural dizziness, wound complication

Vascular disorders: hypertension, hypotension, haematoma, thrombophlebitis, flushing, hot flush

Blood and lymphatic system disorders: anaemia, lymphopenia, haemolysis, leukocytosis, leukopenia, iron deficiency anaemia, neutropenia

Renal and urinary disorders: dysuria, azotaemia, calculus urinary, chromaturia, haematuria, urinary tract disorder

Eye disorders: visual acuity reduced, conjunctivitis, lacrimation increased, ocular hyperaemia, conjunctival haemorrhage, conjunctivitis allergic, dry eye

Reproductive system and breast disorders: breast pain, amenorrhoea, metrorrhagia, breast oedema, genital ulceration

Immune system disorders: hypersensitivity, anaphylactic reaction, drug hypersensitivity

Metabolism and nutrition disorders: decreased appetite, hyperglycaemia, diabetes mellitus, hyperphosphataemia, fluid retention

Cardiac disorders: palpitations, sinus tachycardia

Psychiatric disorders: depression, restlessness, disorientation

Hepatobiliary disorders: hepatitis, hepatic function abnormal, hepatotoxicity

Ear and labyrinth disorders: ear pain, motion sickness, tinnitus, vertigo

Neoplasms benign, malignant and unspecified (including cysts and polyps): basal cell carcinoma, melanocytic naevus, parathyroid tumour benign

Adult PsA Patients Treated with ORENCIA:

ADRs reported in less than 1% of patients receiving ORENCIA in the PsA I Trial and not listed elsewhere in the [8 ADVERSE REACTIONS](#) section are listed below by body system.

Metabolism and nutrition disorders: dyslipidemia, hypercholesterolemia

Respiratory, thoracic and mediastinal disorders: catarrh

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

JIA/JRA Patients Treated with Intravenous ORENCIA:

In Periods A and C of the pediatric trial, the list of less common Adverse Drug Reactions (<1 %) are represented by no more than a single case (by Phase). In the double-blind Period B, where a single ADR case yields an incidence of 1.7%, no ADR with a frequency of less than 1% was reported.

ADRs reported in less than 1% of patients receiving ORENCIA in open-label Phases A and C of the pediatric clinical trial and not listed in Table 4 and Table 6 are listed below by body system.

Blood and lymphatic system disorders: Anaemia, lymphopenia, monocytosis

Gastrointestinal disorders: Abdominal discomfort, abdominal pain upper, gastritis, intestinal villi atrophy, stomach discomfort

General disorders and administration site conditions: Chest pain, chills, influenza like illness, infusion site pain, injection site duration, injection site pain, malaise, pain

Infections and infestations: Body tinea, bronchitis, bronchitis acute, fungal skin infection, furuncle, gastroenteritis, gastroenteritis viral, giardiasis, helicobacter infection, influenza, nail infection, otitis externa, parasitic infection intestinal, paronychia, pharyngitis, pharyngotonsillitis, staphylococcal infection, tinea cruris, tooth abscess, tracheobronchitis, urinary tract infection, varicella, viral infection

Immune system disorders: Hypersensitivity

Injury, poisoning and procedural complications: Seroma

Investigations: Alanine aminotransferase increased, antinuclear antibody positive, DNA antibody positive, white blood cell count decreased

Musculoskeletal and connective tissue disorders: Arthralgia, joint swelling, nodule on extremity

Neoplasms benign, malignant and unspecified (including cysts and polyps): Skin papilloma

Nervous system disorders: Tremor

Renal and urinary disorders: Leukocyturia, proteinuria

Reproductive system and breast disorders: Breast swelling, breast tenderness, genital discharge, vaginal discharge

Skin and subcutaneous tissue disorders: Ecchymosis, eczema, erythema elevatum diutinum, ingrowing nail, rash macular, rash papular, skin hypopigmentation, vitiligo, yellow skin

Vascular disorders: Orthostatic hypotension, pallor

8.5 Post-Market Adverse Reactions

Adverse reactions have been reported during the post-approval use of ORENCIA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to ORENCIA. During postmarketing experience, systemic infusion reactions were similar to that seen in the clinical trial experience with IV ORENCIA with the exception of one case of fatal anaphylaxis. Postmarketing reports of systemic injection reactions (eg, pruritus, throat tightness, dyspnea) have been received following the use of SC ORENCIA.

Cases of non-melanoma skin cancer (including basal cell carcinoma and squamous cell carcinoma) have been reported in patients treated with abatacept. A risk for the development of non-melanoma skin cancer in patients treated with abatacept cannot be excluded.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Formal drug interaction studies have not been conducted with ORENCIA (abatacept).

9.4 Drug-Drug Interactions

Formal drug interaction studies have not been conducted with ORENCIA (abatacept). However, population pharmacokinetic analyses revealed that MTX, non steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and TNF blocking agents did not influence abatacept clearance (see [10.3 Pharmacokinetics](#)). The majority of patients received one or more of the following concomitant

medications with ORENCIA: MTX, NSAIDs, corticosteroids, TNF blocking agents, azathioprine, chloroquine, gold, hydroxychloroquine, leflunomide, sulfasalazine, and anakinra.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Blood Glucose Testing

Parenteral drug products containing maltose can interfere with the readings of blood glucose monitors that use test strips with glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ). The GDH-PQQ based glucose monitoring systems may react with the maltose present in ORENCIA for intravenous infusion, resulting in falsely elevated blood glucose readings on the day of infusion. When receiving ORENCIA through intravenous infusion, 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 nicotinic adenine dinucleotide (GDH-NAD), glucose oxidase, or glucose hexokinase test methods (see [7 WARNINGS AND PRECAUTIONS](#)).

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

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Abatacept, a selective co-stimulation modulator, selectively modulates a key co-stimulatory signal required for full activation of T lymphocytes expressing CD28.

Activated T lymphocytes are found in the synovium of patients with rheumatoid arthritis (RA). They contribute to the pathogenesis of rheumatoid arthritis and other autoimmune diseases. Full activation of T lymphocytes requires two signals provided by antigen presenting cells: recognition of a specific antigen by a T cell receptor (signal 1) and a second, co-stimulatory signal. A major co-stimulatory pathway involves the binding of CD80 and CD86 molecules on the surface of antigen presenting cells to the CD28 receptor on T lymphocytes (signal 2). Abatacept binds specifically to CD80 and CD86 selectively inhibiting this co-stimulatory pathway. Studies indicate that naive T lymphocyte responses are more affected by abatacept than memory T lymphocyte responses.

Studies in vitro and in animal models demonstrate that abatacept attenuates T lymphocyte dependent antibody responses and inflammation. In vitro, abatacept attenuates T lymphocyte activation as measured by decreased proliferation and cytokine production in human lymphocytes. Abatacept decreases antigen specific tumour necrosis factor alpha (TNF α), interferon- γ and interleukin-2 production by T lymphocytes. In a rat collagen induced arthritis model, abatacept suppresses inflammation, decreases anti-collagen antibody production and reduces antigen specific production of interferon- γ .

10.2 Pharmacodynamics

Dose finding studies were conducted with abatacept monotherapy (placebo, 0.5 mg/kg, 2 mg/kg, and 10 mg/kg) and in combination with methotrexate (MTX) (placebo, 2 mg/kg, and 10 mg/kg). In both studies, the ACR response rates increased with increasing doses at 2 mg/kg and 10 mg/kg. In clinical trials with ORENCIA (abatacept) using doses approximating 10 mg/kg, inhibition of T lymphocyte activation, decreases in products of macrophages, fibroblast-like synoviocytes, and B cells, and reductions in acute phase reactants of inflammation were observed.

Decreases were seen in: serum levels of soluble interleukin-2 receptor, a marker of T lymphocyte activation; serum interleukin-6, a product of activated macrophages and fibroblast-like synoviocytes; rheumatoid factor, an autoantibody produced by plasma cells; and C-reactive protein (CRP), an acute phase reactant of inflammation. In addition, serum levels of matrix metalloproteinase-3, which produces cartilage destruction and tissue remodeling, were decreased. Reductions in serum TNF α were also observed. These changes are consistent with the mechanism of action of ORENCIA which modulates upstream events in the inflammatory cascade, preventing downstream production of cytokines or other inflammatory mediators.

10.3 Pharmacokinetics

Healthy Adult Subjects – Intravenous Infusion

Following a single intravenous dose of 10 mg/kg of abatacept in healthy adult subjects, the mean terminal half-life was 16.7 days, ranging from 12 to 23 days. The systemic clearance of abatacept was approximately 0.23 mL/hr/kg. The distribution volume (V_{ss}) ranged from 0.06 to 0.13 L/kg. The maximum serum concentration (C_{max}) of abatacept following this dose was approximately 290 mcg/mL.

Adult Rheumatoid Arthritis Patients – Intravenous Infusion

The pharmacokinetics of abatacept in rheumatoid arthritis patients and healthy subjects appeared to be comparable. After multiple intravenous infusions (days 1, 15, 30, and monthly thereafter), the pharmacokinetics of abatacept in rheumatoid arthritis patients showed proportional increases of C_{max} and AUC over the dose range of 2 mg/kg to 10 mg/kg. At 10 mg/kg, the following pharmacokinetic parameters were observed:

Table 11: Pharmacokinetic Parameters

Parameter	Value	Range
Mean terminal half-life (t _{1/2})	13.1 days	8 - 25 days
Mean distribution volume (V _{ss})	0.07 L/kg	0.02 - 0.13 L/kg
Systemic clearance	~0.22 mL/h/kg	0.13 - 0.47 mL/h/kg
Mean steady-state trough concentrations	~25 mcg/mL	22 - 29 mcg/mL
Mean C _{max} concentrations	~290 mcg/mL	171 - 398 mcg/mL

No systemic accumulation of abatacept occurred upon continued repeated treatment with 10 mg/kg at monthly intervals in rheumatoid arthritis 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 (MTX), nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and TNF blocking agents did not influence abatacept clearance.

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

JIA/JRA – Intravenous Infusion

Serum concentrations of abatacept in children and adolescents (aged 6 to 17 years; n=186) with JIA/JRA were measured following intravenous infusion of 10 mg/kg abatacept on Days 1, 15, and 29, and every 28 days thereafter for up to 40 weeks. The mean (range) trough serum concentration of abatacept at steady-state was 11.9 (0.15 to 44.6) mcg/mL. Population pharmacokinetic analyses of the serum concentration data showed that clearance of abatacept increased with baseline body weight. The estimated mean (range) clearance of abatacept in the JIA/JRA patients was 0.40 (0.20 to 1.12) mL/h/kg. After accounting for the effect of body weight, the clearance of abatacept was not related to age and gender. Concomitant methotrexate, corticosteroids, and NSAIDs were also shown not to influence abatacept clearance.

Adult RA - Subcutaneous Administration

Abatacept exhibited linear pharmacokinetics following subcutaneous administration. The bioavailability of abatacept following subcutaneous administration relative to IV infusion is 78.6%. 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 SC and IV administration.

Systemic exposure as measured by steady-state C_{max} and AUC was lower following 125 mg weekly SC administration compared to the monthly IV administration regimen in RA subjects (48.1 vs. 231.6 mcg/mL for C_{max}; 5875.5 vs. 41981.5 mcg*h/mL for AUC), but the mean C_{min} at steady state was higher for SC vs. IV administration (32.5 vs. 22.3 mcg/mL, respectively). A single study was conducted to determine the effect of monotherapy use of ORENCIA on immunogenicity following subcutaneous administration without an IV load. When the IV loading dose was not administered, steady-state trough serum concentrations of 22.6 mcg/mL were achieved after 6 to 8 weeks of weekly SC abatacept administration, and a mean trough concentration of 12.6 mcg/mL was achieved after 2 weeks of dosing. The efficacy response over time in this study appeared consistent with studies that included an IV loading dose, however the effect of no IV load on the onset of efficacy has not been formally studied.

Consistent with the IV data, population pharmacokinetic analyses for SC abatacept 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 apparent clearance. Concomitant treatment with MTX, NSAIDs or corticosteroids did not affect abatacept apparent clearance.

Adult Psoriatic Arthritis - Intravenous and Subcutaneous Administration

In Study PsA-II (a dose ranging study), following monthly IV administration of abatacept, the steady-state of abatacept was dose-related. The geometric mean (CV%) C_{min} at Day 169 were 7.8 mcg/mL (56.3%), 24.3 mcg/mL (40.8%), and 26.6 mcg/mL (39.0%), for the 3/3 mg/kg, 10/10 mg/kg, and 30/10 mg/kg monthly dose regimens, respectively. In Study PsA-I following weekly SC administration of abatacept at 125 mg, steady-state of abatacept was reached at Day 57 with the geometric mean (CV%) trough concentrations (C_{min}) ranging from 22.3 (54.2%) to 25.6 mcg/mL (47.7%) on Days 57 to 169, respectively.

Consistent with the RA results, population pharmacokinetic analyses for abatacept in psoriatic arthritis patients revealed that there was a trend toward higher clearance (L/h) of abatacept with increasing body weight. In addition, relative to the RA patients with the same body weight, abatacept clearance in psoriatic arthritis patients was approximately 8% lower, resulting in higher abatacept exposures in patients with PsA. This slight difference in exposures, however, is not considered to be clinically meaningful.

Prophylaxis of Acute Graft versus Host Disease – Intravenous Administration

In a study of prophylaxis of acute Graft Versus Host Disease (aGVHD) patients aged 6 years and older, the geometric mean (%CV) trough concentrations of abatacept after 4 doses utilizing weight-based dosing of approximately 10 mg/kg administered on the day before transplantation (Day -1), followed by a dose on Day 5, 14, and 28 after transplant, were 22.5 mcg/mL (243.9 %CV) and 31.1 mcg/mL (114.4 %CV) for matched unrelated donors (URD) and mismatched URD, respectively, on Day 63.

Table 12: Pharmacokinetic Parameters (Mean, Range) in Subjects Undergoing HSCT from a Matched or 1 Allele-Mismatched Unrelated Donor in Study GVHD-1

PK Parameter	7 of 8 Cohort n=42	8 of 8 Cohort n=73
Minimum Concentration (C _{min}) ^a [mcg/mL]	59 (26-112)	43 (25-73)
Peak Concentration (C _{max}) [mcg/mL]	221 (163-292)	172 (107-254)
Terminal half-life (t _{1/2}) [days]	20.6 (6-43)	20.8 (12-38)
Systemic clearance (CL) [mL/h/kg]	0.26 (0.15-0.65)	0.32 (0.18-0.56)
Volume of distribution (V _{ss}) [L/kg]	0.13 (0.08-0.27)	0.17 (0.11-0.26)

^a C_{min} observed on Day 5 of the treatment period; n = 18 for the 7/8 Cohort; n = 32 for the 8/8 Cohort.

C_{max}, t_{1/2}, CL, and V_{ss} are model predicted after first 10 mg/kg ORENCIA intravenous infusion.

Population pharmacokinetic analyses in patients with aGVHD demonstrated that 7 of 8 HLA-matched HSCT recipients had 29% lower clearance compared to 8 of 8 HLA-matched HSCT recipients. Consistent with previous data, increasing body weight was associated with higher clearance of abatacept, while age (when corrected for body weight) did not affect apparent clearance. Concomitant medication, such as methotrexate and calcineurin inhibitors (e.g., cyclosporine and tacrolimus), did not influence abatacept clearance.

11 STORAGE, STABILITY AND DISPOSAL

Lyophilized Powder for solution (intravenous administration)

ORENCIA (abatacept) lyophilized powder must be refrigerated at 2°C to 8°C. 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 (see [4 DOSAGE AND ADMINISTRATION](#)).

Solution (subcutaneous administration)

ORENCIA Injection Solution (prefilled syringe) must be refrigerated at 2°C to 8°C. Do not use beyond the expiration date on the syringe. Protect from light by storing in the original package until time of use. Do not freeze.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: abatacept

Molecular weight: Abatacept has an average mass of approximately 92,300 Daltons as determined by matrix-assisted laser desorption-ionization time of flight (MALDI-TOF) mass spectrometry. The measured molecular weight is greater than the theoretical value predicted by the cDNA-derived amino acid sequence owing to post-translational glycosylation.

Structural formula: Abatacept is a fusion protein comprised of the extracellular domain of human Cytotoxic T-Lymphocyte Antigen-4 (CTLA4) and part of a human immunoglobulin G constant region (C1), containing the hinge, CH2 and CH3 domains. Abatacept is comprised of two homologous glycosylated polypeptide chains of 357 amino acids each. It exists as a covalent homodimer (referred to as abatacept “monomer”) linked through an inter-chain disulfide bond.

Physicochemical properties:

- Physical Form: A buffered aqueous solution of abatacept drug substance (50 mg/mL in 25 mM sodium phosphate, 50 mM sodium chloride, pH 7.5) is visually clear, colorless to pale yellow, and is essentially free from any visible particulate matter.
- Solubility: Abatacept solution up to 100 mg/mL concentration is visually clear but may appear hazy when observed under a light intensity of ≥ 5 K lux. These solutions can be sterile-filtered through a 0.2 μm filter with no apparent loss in protein concentration.
- Solution pH: The pH of the abatacept drug substance solution is 7.5 ± 0.5 pH. Multiple charged isoforms in the native abatacept drug substance ranging from pI 4.5 - 5.5 are detected using isoelectric focusing (IEF).
- Extinction Coefficient: The extinction coefficient for abatacept was calculated to be $92886 \text{ M}^{-1}\text{cm}^{-1}$.

Product Characteristics:

Lyophilized Powder for Intravenous Infusion

Abatacept for Injection, 250 mg/vial, is a lyophilized formulation which is constituted with Sterile Water for Injection, USP and further diluted using 0.9% Sodium Chloride Injection, USP, for administration by intravenous infusion.

Solution for Subcutaneous Administration

The subcutaneous solution in prefilled syringes is clear, colorless to pale yellow with a pH of 6.8 to 7.4. Each single dose of subcutaneous injection provides 125 mg abatacept, 170 mg sucrose, 8 mg poloxamer 188, 0.286 mg monobasic sodium phosphate monohydrate, 0.838 mg dibasic sodium phosphate anhydrous, and up to 1 mL water for injection. ORENCIA injection for subcutaneous administration contains no maltose.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Adult Rheumatoid Arthritis:

The efficacy and safety of ORENCIA (abatacept) for intravenous infusion were assessed in six randomized, double-blind, controlled studies (five placebo-controlled and one active-controlled) in patients \geq age 18 with active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR) criteria. ORENCIA was given as a 30-minute intravenous infusion at weeks 0, 2, and 4 and then every 4 weeks thereafter. Study IM101-174 was a large (n=1457) 6-month controlled randomized, double-blind, double-dummy non-inferiority study that compared the efficacy and safety of abatacept administered subcutaneously (SC) and intravenously (IV) in subjects with rheumatoid arthritis (RA), receiving methotrexate (MTX), and experiencing an inadequate response to MTX (MTX-IR). Patients were stratified by body weight (<60kg, 60 to 100 kg and >100kg), randomized in a double-blind manner 1:1 ratio to either SC abatacept 125 mg weekly (fixed-dose SC plus an IV abatacept loading dose by weight at Day 1) or abatacept IV infusion by weight on Days 1, 15, 29, and then every 28 days. Patients continued taking their current dose of MTX. In both groups at baseline, the mean age was 50 years, the mean disease duration was 8 years, the mean tender joint count was 30, the mean swollen joint count was 20, and the mean body weight was 72 kg (range 36.5 to 169.8 kg).

After the first 6 months of the Study, 659 (95.8%) patients from the original SC group and 642 (96%) patients from the original IV abatacept group entered the open-label long-term period of the study and continue to receive SC abatacept.

The primary objective of the study was to demonstrate in patients with active RA and inadequate response to MTX, that after 6 months of treatment with either SC injections or IV infusions of abatacept, treatment with SC abatacept +MTX was non-inferior to IV abatacept +MTX in ACR 20 responses. The non-inferiority margin of 7.5% was defined only for the primary endpoint (ACR 20 at 6 months.)

Table 13 summarizes the controlled clinical studies in patients with active rheumatoid arthritis.

Table 13: Summary of Controlled Clinical Trials Supporting Efficacy and Safety in Patients with Rheumatoid Arthritis

Study no.	Trial design	Dosage Dosing Schedule Route of Administration	Study subjects (n) ^b	Mean age (SD)	Gender (% Female)
IM103002	Randomized, double-blind, placebo- controlled study	Abatacept 0.5, 2, and 10 mg/kg Days 1, 15, 29, and 57 IV	90	48.3 (12.5)	74
		Abatacept Placebo	32	48.3 (11.7)	81
IM101100	Randomized, double-blind, placebo- controlled study	Abatacept 2 and 10 mg/kg IV Days 1, 15, 29, and every 4 weeks thereafter	220	55.2 (12.0)	69
		Abatacept Placebo	119	54.7 (12.0)	66

	Open-label extension	Abatacept 10 mg/kg IV every 4 weeks	219	54.6 (12.0)	68
AIM ^a	Randomized, double-blind, placebo-controlled study	Abatacept fixed dose IV Days 1, 15, 29, and every 4 weeks thereafter			
		Abatacept	433	51.5 (12.9)	78
	Placebo	219	50.4 (12.4)	82	
	Open-label extension	Abatacept 10 mg/kg IV every 4 weeks	539	50.8 (12.4)	79
ATTAIN ^a	Randomized, double-blind, placebo-controlled study	Abatacept fixed dose IV Days 1, 15, 29, and every 4 weeks thereafter			
		Abatacept	258	53.4 (12.4)	77
	Placebo	133	52.7 (11.3)	80	
	Open-label extension	Abatacept 10 mg/kg IV every 4 weeks	317	52.9 (11.7)	78
ASSURE ^a	Randomized, double-blind, placebo-controlled study	Abatacept fixed dose IV Days 1, 15, 29, and every 4 weeks thereafter			
		Abatacept	959	52.4 (11.7)	82
		Placebo	482	52.1 (12.0)	83
AGREE ^a	Randomized, double-blind, active-controlled study	Abatacept fixed dose IV Days 1, 15, 29, and every 4 weeks thereafter			
		Abatacept + MTX	256	50.1 (12.4)	77
		MTX+placebo	253	49.7 (13.0)	79
IM101174 ^a	Randomized, double-blind, double-dummy, placebo-controlled study	SC abatacept, 125 mg, administered weekly (following IV abatacept loading dose on Day 1) plus IV placebo on Days 1, 15, 29 and every 28 days thereafter	736	49.9 (13.2)	84.4
		IV abatacept Days 1, 15, 29, and every 28 days thereafter plus SC placebo, given weekly	721	50.1 (12.6)	80.4

^a For AIM, ATTAIN, ASSURE, AGREE and IM101-174, the dose was as follows: patients weighing < 60 kg received 500 mg, patients weighing 60 kg to 100 kg received 750 mg, and patients weighing > 100 kg received 1 gram.

^b All randomized and treated subjects.

IM103002 evaluated ORENCIA as monotherapy in 122 patients with active RA who had failed at least one non-biologic, disease-modifying, anti-rheumatic drug (DMARD) or etanercept. Patients were required to have at least 12 tender and 10 swollen joints at randomization and were randomized to receive one of

three doses of ORENCIA (0.5, 2, or 10 mg/kg) or placebo ending at week 8.

In IM101100 and in the AIM study, the efficacy and safety of ORENCIA were assessed in patients with an inadequate response to MTX who had at least 12 tender and 10 swollen joints. In the ATTAIN study, the efficacy and safety of ORENCIA were assessed in patients with an inadequate response to a Tumor Necrosis Factor (TNF) blocking agent who had at least 12 tender and 10 swollen joints. The ASSURE study assessed primarily safety in patients with active rheumatoid arthritis requiring additional intervention in spite of current therapy with disease-modifying anti-rheumatic drugs (DMARDs) or biologic RA agents. Patients in ASSURE could have had co-morbid medical conditions, such as diabetes mellitus, asthma, chronic obstructive pulmonary disease, or congestive heart failure. The AGREE study evaluated the efficacy and safety of ORENCIA in MTX-naïve patients with early, erosive RA (≤ 2 years disease duration). Patients were required to have at least 12 tender and 10 swollen joints at randomization. In AGREE, patients previously naïve to MTX were randomized to receive ORENCIA plus MTX or MTX plus placebo.

IM101100 evaluated 339 patients with active rheumatoid arthritis who were on a stable dose of MTX (median dose 15 mg/week). For all patients randomized and treated in the 10 mg/kg and placebo groups of this study, the median age was 55 years, the median disease duration was 6 years, and the median tender and swollen joint counts were 28 and 20, respectively. Patients were randomized to receive one of two doses of ORENCIA (2 or 10 mg/kg) or placebo for 12 months. The primary endpoint was reduction in signs and symptoms at 6 months as measured by the ACR 20 response. An additional endpoint was improvement in physical function at 12 months as measured by the disability index of the modified Health Assessment Questionnaire.

The AIM study (Abatacept in Inadequate Responders to Methotrexate) evaluated 638 patients with active rheumatoid arthritis who were on a stable dose of MTX (median dose 15 mg/week). For all patients randomized and treated, the median age was 52 years, the median disease duration was 7 years, and the median tender and swollen joint counts were 29 and 20, respectively. Patients were randomized to receive a fixed dose approximating 10 mg/kg of ORENCIA or placebo for 12 months. The dose of ORENCIA was 500 mg for patients weighing less than 60 kg, 750 mg for patients weighing 60 to 100 kg, and 1 gram for patients weighing greater than 100 kg (see [4 DOSAGE AND ADMINISTRATION](#)). The primary endpoints were reduction in signs and symptoms at 6 months as measured by the ACR 20 response, inhibition of the progression of structural damage at 12 months as assessed by the Genant-modified Sharp scoring of radiographs, and improvement in physical function at 12 months as measured by the disability index of the Health Assessment Questionnaire.

The ATTAIN study (Abatacept Trial in Treatment of Anti-TNF Inadequate Responders) evaluated 389 patients with active rheumatoid arthritis who had an inadequate response to the TNF blocking agents, etanercept or infliximab. Patients discontinued these agents prior to randomization and were monitored for flare. Patients did not flare following discontinuation. All patients were required to take a DMARD. For all patients randomized and treated, the median age was 54 years, the median disease duration was 11 years, and the median tender and swollen joint counts were 30 and 20, respectively. Concurrent DMARDs included one or more of the following: MTX, azathioprine, chloroquine, gold, hydroxychloroquine, leflunomide and sulfasalazine. Concurrent use of the biologic agent anakinra was also permitted. Patients were randomized to receive a fixed dose of ORENCIA (as defined above) or placebo for 6 months. The primary endpoints at 6 months were reduction in signs and symptoms as measured by the ACR 20 response and improvement in physical function as measured by the disability

index of the Health Assessment Questionnaire.

The ASSURE study (Abatacept Study of Safety in Use with Other RA Therapies) assessed the safety of ORENCIA in 1441 patients with active rheumatoid arthritis receiving concurrent DMARDs or biologic agents. For patients in this study, the median age was 52 years and the median disease duration was 7 years. This study included patients with co-morbid conditions such as diabetes mellitus, asthma, chronic obstructive pulmonary disease, or congestive heart failure. Concurrent DMARDs included one or more of the following: MTX, azathioprine, chloroquine, gold, hydroxychloroquine, leflunomide and sulfasalazine. Concurrent biologic agents included adalimumab, anakinra, etanercept, and infliximab. Patients were randomized to receive a fixed dose of ORENCIA (as defined above) or placebo for 12 months. In addition to safety, improvement in physical function at 12 months was assessed using the disability index of the Health Assessment Questionnaire.

The AGREE study evaluated 509 MTX-naïve subjects, serum rheumatoid factor and/ or anti-Cyclic Citrullinated Peptide 2 (Anti-CCP2)- positive subjects with early, erosive RA. For all patients randomized and treated, the median age was 51 years, the median disease duration was 3 months and the median tender and swollen joint counts were 28 and 20, respectively. Patients were randomized to receive abatacept (10 mg/kg, weight-tiered dose) plus MTX or MTX plus placebo for the first 12 months of treatment. In both groups, the MTX dose was titrated to at least 15 mg per week not to exceed 20 mg per week. To minimize potential MTX toxicity, all subjects also received either folic acid, folinic acid, or leucovorin according to the manufacturer recommendations. After the first 12 months of treatment, all subjects received the combination of abatacept+MTX. The co-primary endpoints of this study were the proportion of subjects in abatacept+MTX group versus placebo+MTX who achieved DAS-28-CRP remission and to compare inhibition of joint damage progression measured by the Genant-modified Sharp total score at 12 months of treatment.

In Study IM101-174, the goal was to demonstrate non-inferiority of the efficacy and safety of ORENCIA subcutaneous relative to intravenous infusion in subjects with moderate to severely active RA and experiencing inadequate response to MTX. For all patients randomized and treated, the mean age was 50 years, the mean disease duration was 8 years and the mean tender and swollen joint counts were 30 and 20, respectively, in both groups. ORENCIA was given subcutaneously to patients stratified by body weight (<60 kg, 60 to 100 kg, >100 kg) after a single loading dose of IV and then every week thereafter. Subjects continued taking their current dose of MTX from the day of randomization. The primary endpoint at 6 months was the reduction in signs and symptoms as measured by the ACR 20 response. The ACR 50, ACR 70 and HAQ were also assessed.

Clinical Response

In the IM103002 monotherapy study, the percent of ORENCIA treated patients (n=32) achieving ACR responses at month 3 at a dose of 10 mg/kg (ORENCIA vs placebo) was 53% vs 31% (ACR 20), 16% vs 6% (ACR 50) and 6% vs 0 (ACR 70). The results are summarized in Table 14.

Table 14: ACR Responses in Placebo-Controlled Trial with Intravenous ORENCIA (Study IM103002)

Response Rate at Month 3	Percent of Patients	
	Inadequate Response to DMARDs	
	ORENCIA (10 mg/kg) n=32	Placebo n=32
ACR 20	53%	31%
ACR 50	16%	6%
ACR 70	6%	0

The percent of ORENCIA treated patients achieving ACR 20, 50, and 70 responses in IM101100, AIM and ATTAIN are shown in Table 15. In subjects with an inadequate response to MTX (IM101100 and AIM) and in those with an inadequate response to a TNF blocking agent (ATTAIN), ORENCIA treated patients had higher response rates in ACR 20, 50, and 70 at 6 months compared to placebo treated patients. In Studies IM101100 and AIM, ACR 20, 50, and 70 response rates at 12 months were greater in ORENCIA treated patients as compared to placebo patients.

Table 15: ACR Responses in Placebo-Controlled Trial with Intravenous ORENCIA (Study IM101100, AIM, ATTAIN)

Response Rate	Percent of Patients					
	Inadequate Response to MTX				Inadequate Response to TNF Blocking Agents	
	IM101100		AIM		ATTAIN	
	ORENCIA ^a + MTX n = 115	Placebo + MTX n = 119	ORENCIA ^b + MTX n = 424	Placebo + MTX n = 214	ORENCIA ^b + DMARDs ^c n = 256	Placebo + DMARDs ^c n = 133
ACR 20						
Month 6	61% ^d	35%	68% ^d	40%	50% ^d	20%
Month 12	63% ^d	36%	73% ^d	40%	NA ^f	NA ^f
ACR 50						
Month 6	37% ^d	12%	40% ^d	17%	20% ^d	4%
Month 12	42% ^d	20%	48% ^d	18%	NA ^f	NA ^f
ACR 70						
Month 6	17% ^d	2%	20% ^d	7%	10% ^e	2%
Month 12	21% ^e	8%	29% ^d	6%	NA ^f	NA ^f

^a 10 mg/kg

^b Fixed dose (see [4 DOSAGE AND ADMINISTRATION](#))

^c Concurrent DMARDs included one or more of the following: MTX, azathioprine, chloroquine, gold, hydroxychloroquine, leflunomide and sulfasalazine. Concurrent use of the biologic agent anakinra was also permitted.

^d p < 0.001, ORENCIA vs. Placebo

^e p < 0.01, ORENCIA vs. Placebo

^f After 6 months, patients were given the opportunity to enter into an open-label study.

In Study IM101-174, ORENCIA administered subcutaneously (SC) was non-inferior relative to intravenous (IV) infusions of ORENCIA with respect to ACR20 responses at 6 months. The proportion of patients with an ACR 20 response at Day 169 was 76.1% in the SC abatacept group and 75.7% in the IV abatacept group (difference = 0.4%; 95% CI: -4.2, 4.8). Such results were consistent with those in the ITT population.

Table 16: ACR Responses in Controlled Trial with subcutaneous ORENCIA (IM101-174)

Response Rate	Percent of Patients	
	Inadequate Response to MTX	
	ORENCIA ^a SC + MTX n = 693	ORENCIA ^a IV + MTX n = 678
ACR 20		
Month 3	68%	69%
Month 6	76%	76%

^a Per protocol data is presented in table. For ITT; n=736, 721 for SC and IV Orenicia, respectively

At 6 months ACR50 response was observed in 52% of patients in ORENCIA SC+MTX group and 50% of patients in ORENCIA IV+MTX group, respectively.

In the studies with intravenous ORENCIA, subjects had a high degree of activity at baseline and a mean duration of rheumatoid arthritis of approximately 10 years. The results of the components of the ACR response criteria for studies IM101100, AIM, ATTAIN are shown in Table 17. In patients treated with ORENCIA, improvement was seen in all components through 6 and 12 months.

Table 17: Components of ACR Response

	Inadequate Response to MTX				Inadequate Response to TNF Blocking Agents	
	IM101100		AIM		ATTAIN	
	ORENCIA ^a + MTX n = 115	Placebo + MTX n = 119	ORENCIA ^b + MTX n = 424	Placebo + MTX n = 214	ORENCIA ^b + DMARDs ^c n = 256	Placebo + DMARDs ^c n = 133
Number of tender joints (0-68)						
Baseline	29	28	28	31	30	31
Month 6	9 ^d	16	7 ^d	14	13 ^d	24
Month 12	5 ^d	16	6 ^d	14	NA ^e	NA ^e
Number of swollen joints (0-66)						
Baseline	20	21	19	20	21	20
Month 6	8 ^d	13	5 ^d	14	13 ^d	24
Month 12	6 ^d	11	4	10	NA ^e	NA ^e

Pain^f						
Baseline	66	72	67	70	73	74
Month 6	26 ^d	48	27 ^d	50	43 ^g	64
Month 12	24 ^d	46	23 ^d	48	NA ^e	NA ^e
Patient global assessment^f						
Baseline	60	65	66	64	71	73
Month 6	29 ^g	46	29 ^d	48	44 ^d	63
Month 12	27 ^h	46	23 ^d	45	NA ^e	NA ^e
Disability index						
Baseline	1.00 ⁱ	1.00 ⁱ	1.75 ^j	1.75 ^j	1.88 ^j	2.00 ^j
Month 6	0.50 ^{d,i}	0.75 ⁱ	1.13 ^{d,j}	1.38 ^j	1.38 ^j	1.75 ^j
Month 12	0.50 ^{d,i}	0.88 ⁱ	1.00 ^{d,j}	1.38 ^j	NA ^e	NA ^e
Physician global assessment^f						
Baseline	62	65	69	68	71	69
Month 6	25 ^d	45	21 ^d	40	32 ^d	54
Month 12	22 ^d	47	17 ^d	38	NA ^e	NA ^e
CRP (mg/dL)						
Baseline	2.0	2.1	2.2	2.1	3.4	2.8
Month 6	1.0 ^d	1.9	0.9 ^d	1.8	1.3 ^d	2.3
Month 12	0.9 ^d	2.1	0.8 ^d	1.7	NA ^e	NA ^e

^a 10 mg/kg

^b Fixed dose (see [4 DOSAGE AND ADMINISTRATION](#))

^c Concurrent DMARDs included one or more of the following: MTX, azathioprine, chloroquine, gold, hydroxychloroquine, leflunomide and sulfasalazine. Concurrent use of the biologic agent anakinra was also permitted.

^d $p < 0.001$, ORENCIA vs. placebo, based on mean percent change from baseline.

^e After 6 months, patients were given the opportunity to enter into an open-label study.

^f Visual analog scale; 0 - best, 100 - worst.

^g $p < 0.01$, ORENCIA vs. placebo, based on mean percent change from baseline.

^h $p < 0.05$, ORENCIA vs. placebo, based on mean percent change from baseline.

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

^j Health Assessment Questionnaire; 0 = best, 3 = worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

Among patients receiving ORENCIA in Studies AIM and ATTAIN, statistically significant differences in the ACR 20 response versus placebo were observed after administration of the first dose, as measured at day 15. These differences remained significant for the duration of the studies.

The ACR 20, 50 and 70 responses for Studies AIM and ATTAIN are shown in Figure 1 and Figure 2,

respectively. The ACR 50 response with ORENCIA was significantly greater than placebo at months 2 and 3, respectively, for Studies AIM and ATTAIN, with continued improvement in the ACR 50 response rate until double-blind study completion. The ACR 70 response with ORENCIA was significantly greater than placebo at months 3 and 2, respectively, for Studies AIM and ATTAIN, with progressive improvement in the ACR 70 response rate until study completion.

In the AGREE study, subjects treated with abatacept+MTX had improvements in ACR 20, ACR 50 and ACR 70 of 76%, 57%, and 43% respectively and subjects treated with MTX+placebo had improvements in ACR 20, ACR 50 and ACR 70 of 62%, 42%, and 27% respectively at Month12 and the differences in all cases were significant.

Figure 1

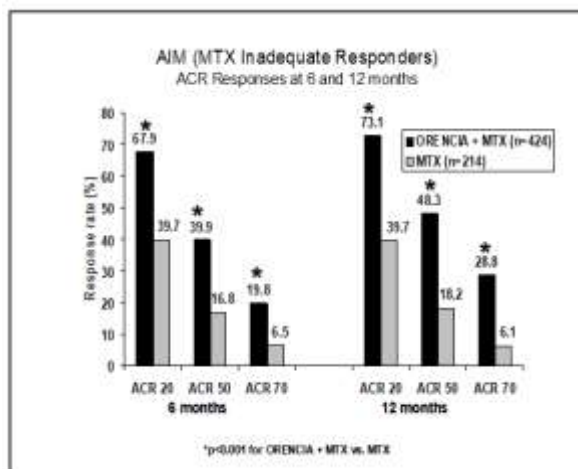
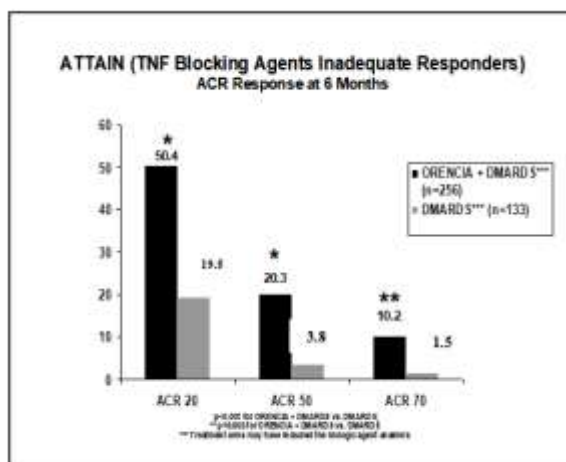


Figure 2



Major clinical response, defined as continuous ACR 70 response over a 6-month period, was measured in AIM and AGREE. In the AIM study, among ORENCIA treated patients, 14% achieved a major clinical response, as compared with 2% in placebo patients. In addition, 6% of ORENCIA treated patients in this 12-month study achieved an extended major clinical response (continuous ACR 70 response over 9 months), as compared with 0.5% in placebo patients. In the AGREE study, among ORENCIA+MTX treated patients, 27% achieved a major clinical response, as compared with 12% in MTX+placebo patients.

All subjects who completed the double-blind portion of studies IM101100 (Days 1 through Day 360), IM101102 (Days 1 through Day 365) and IM101029 (Day 1 through Day 169) were eligible to continue into the long-term open label portion of these studies. All subjects who were enrolled in the open-label periods received a fixed dose of abatacept (that approximated 10 mg/kg) in combination with MTX or other DMARD. As needed, the use of additional DMARDs or change in the corticosteroids, MTX, and NSAIDs dosages was permitted.

In study IM101100, ACR 20 responses were observed in 71% (42/59) of abatacept group patients, ACR 50 in 41% (24/59), and ACR 70 31% (18/58) at 48 months. In study IM101029 (ATTAIN), 217 patients entered the open label extension. ACR-20 responses were observed in 56% (122/217) patients, ACR-50 in 33% (72/217) and ACR 70 in 16% (35/217) at 24 months. In study IM101102 (AIM), 376 abatacept group patients entered the open label extension. ACR-20 responses were observed in 80% (302/376), ACR 50 in 56% (209/376) and ACR 70 in 34% (129/376) at 24 months.

Remission

ORENCIA was significantly better than placebo in other measures of rheumatoid arthritis disease activity not included in the ACR response criteria, such as morning stiffness. The level of disease activity was also assessed using the Disease Activity Score 28 (DAS28).

In the AIM study, a DAS28-defined remission (DAS28 <2.6) was achieved in 15% and 24% of ORENCIA treated patients compared with 3% and 2% of placebo patients at 6 months and 12 months, respectively (Figure 4). In the open label extension of the AIM study, DAS28-defined remission was observed in 31% (102/330) of patients at 24 months. In ATTAIn, DAS28-defined remission was observed in 10% of ORENCIA treated patients compared with 1% of placebo patients at 6 months (Figure 5). In the open label extension of the ATTAIn study, DAS28-defined remission was observed in 21% (31/151) patients at 24 months. In AGREE, DAS28-defined remission was achieved in 41% (106/256) of ORENCIA+MTX treated patients compared with 23% (59/253) of MTX+placebo patients at 12 months.

Figure 3

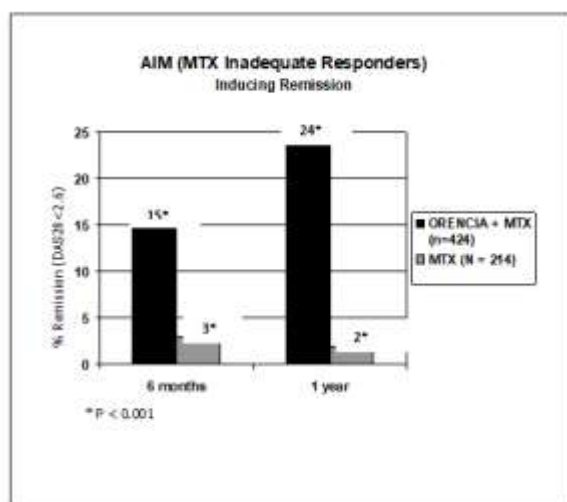
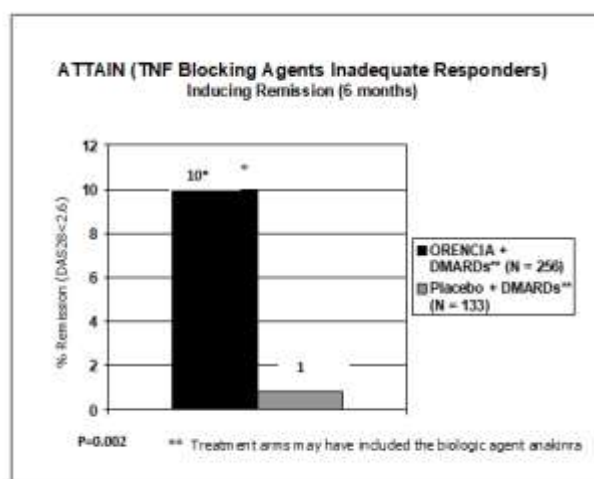


Figure 4



Radiographic Response

Structural joint damage was assessed radiographically and expressed as change in Genant-modified Sharp Total Score and its components, the erosion score and Joint Space Narrowing (JSN) score. In AIM at baseline, radiographic parameters were similar between treatment groups. ORENCIA/MTX significantly inhibited the progression of structural damage compared to MTX alone after 12 months of treatment as shown in Table 18. The benefits of ORENCIA/MTX compared to placebo/MTX were observed regardless of disease duration, including in patients with disease duration of less than 2 years through greater than 10 years.

Table 18: Mean Radiographic Changes Over 12 Months in AIM

Parameter	ORENCIA/MTX n = 391	Placebo/ MTX n = 195	Placebo/MTX - ORENCIA/MTX (95% CI)	P-value ^a
Total sharp score	1.21	2.32	1.11 (0.35, 1.88)	0.012

Erosion score	0.63	1.14	0.51 (0.08, 0.94)	0.029
JSN score	0.58	1.18	0.60 (0.21, 0.99)	0.009

^a Based on non-parametric analysis

In the open-label extension of the AIM study, 75% (324/433) of patients initially randomized to ORENCIA/MTX were evaluated radiographically by the TSS. In fifty (50) percent (163/324) of these patients who entered the open-label extension, no progression of structural damage as defined by a change in the TSS of zero or less was observed at 24 months.

In the AGREE study, the mean change in TSS at 12 months was significantly lower in patients treated with ORENCIA+MTX compared to those treated with MTX+placebo.

Table 19: Mean Radiographic Changes Over 12 Months in AGREE

Parameter	ORENCIA/MTX n = 242	Placebo/ MTX n = 242	Placebo/MTX - ORENCIA/MTX (95% CI)	P-value ^a
Total sharp score	0.63	1.06	0.44 (0.06, 0.82)	0.040
Erosion score	0.50	0.89	0.40 (0.07, 0.74)	0.033
JSN score	0.13	0.17	0.04 (-0.05, 0.14)	0.353

^a Based on non-parametric analysis

Although the treatment comparison for the Total sharp score is statistically significant (p-value = 0.04), the estimated treatment effect of 1.6 structural damage units was not demonstrated in the clinical trial.

Physical Function Response

Improvement in physical function was measured by the Health Assessment Questionnaire Disability Index (HAQ-DI). In studies IM101100, AIM, ATTAIN, ASSURE and AGREE, ORENCIA-treated patients demonstrated significantly greater improvement from baseline than placebo or MTX treated patients in the HAQ-DI. In Study IM101174 improvement from baseline as measured by HAQ-DI at 6 months was observed in 69.8% of patients in ORENCIA SC+MTX group and 65% of patients in ORENCIA IV+MTX group, respectively. The results from IM101100, AIM and ATTAIN are shown in Table 20. Similar results were observed in ASSURE. During the open label period of study IM101100, the improvement in physical function has been maintained for up to 3 years (as-observed analysis).

In the open label extension of the study IM101100, the HAQ response was observed in 53% (31/59) ORENCIA-treated patients at 4 years. In the open-label extension studies of the AIM and ATTAIN, the HAQ response at 24 months was observed in 67% (251/376) patients and in 48% (104/217) respectively.

Table 20: Mean Improvement from Baseline in Physical Function

HAQ Disability Index	Inadequate Response to Methotrexate								Inadequate Response to TNF Blocking Agents			
	IM101100				AIM				ATTAIN			
	ORENCIA ^a + MTX		Placebo + MTX		ORENCIA ^b + MTX		Placebo + MTX		ORENCIA ^b + DMARDs ^c		Placebo + DMARDs ^c	
<i>Mean baseline</i>												
	0.98 ^d	n = 115	0.97 ^d	n = 119	1.69 ^e	n = 422	1.69 ^e	n = 212	1.83 ^e	n = 249	1.82 ^e	n = 130
<i>Mean improvement from baseline</i>												
Month 6	0.40 ^{d,f}	n = 113	0.19 ^d	n = 118	0.59 ^{e,f}	n = 420	0.40 ^e	n = 211	0.45 ^{e,f}	n = 249	0.11 ^e	n = 130
Year 1	0.40 ^{d,f}	n = 115	0.15 ^d	n = 119	0.66 ^{e,f}	n = 422	0.37 ^e	n = 212	NA		NA	

^a 10 mg/kg

^b Fixed dose (see [4 DOSAGE AND ADMINISTRATION](#))

^c Concurrent DMARDs included one or more of the following: MTX, azathioprine, chloroquine, gold, hydroxychloroquine, leflunomide and sulfasalazine. Concurrent use of the biologic agent anakinra was also permitted.

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

^e Health Assessment Questionnaire; 0 = best, 3 = worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

^f p <0.001, ORENCIA vs. placebo.

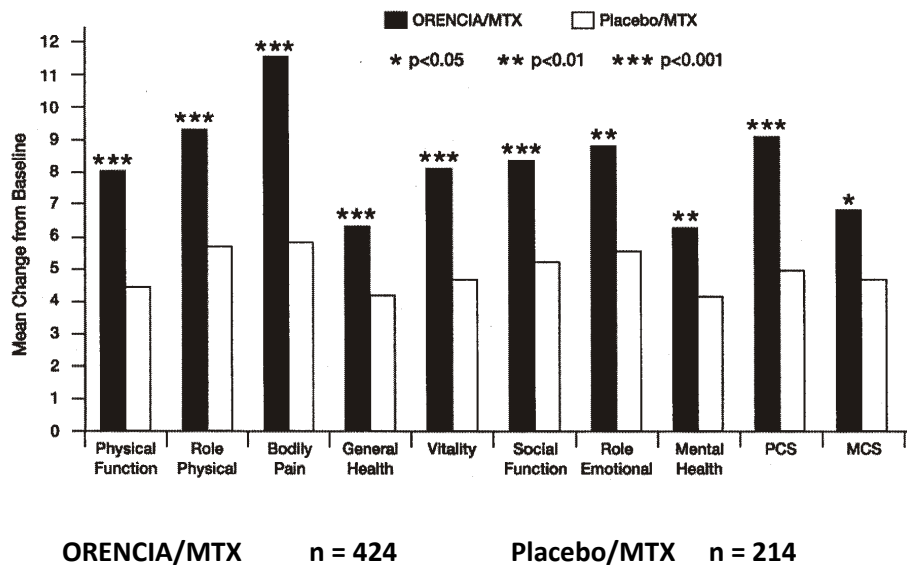
Health-Related Outcomes and Quality of Life

Health-related quality of life was assessed by the SF-36 questionnaire at 6 months in IM101100, AIM and ATTAIN and at 12 months in IM101100 and AIM. In these studies, clinically and statistically significant improvement was observed in the ORENCIA group as compared with the placebo group in all 8 domains of the SF-36 as well as the Physical Component Summary (PCS) and the Mental Component Summary (MCS). In AGREE, improvement was observed at 12 months in the ORENCIA+MTX group as compared with the MTX+placebo group in both PCS and MCS.

The results from AIM are shown in Figure 5.

Figure 5

Significant Improvement in Health-Related Quality of Life (SF-36) at Month 12 in AIM



Juvenile Idiopathic Arthritis/Juvenile Rheumatoid Arthritis:

The safety and efficacy of ORENCIA were assessed in a three-part study including an open-label extension in children with polyarticular juvenile idiopathic arthritis (JIA). Patients 6 to 17 years of age (n=190) with moderately to severely active polyarticular JIA who had an inadequate response to one or more DMARDs, such as MTX or TNF antagonists, were treated. Patients had a disease duration of approximately 4 years with moderately to severely active disease at study entry, as determined by baseline counts of active joints (mean, 16) and joints with loss of motion (mean, 16); patients had elevated C-reactive protein (CRP) levels (mean, 3.2 mg/dL) and ESR (mean, 32 mm/h). The patients enrolled had subtypes of JIA that at disease onset included Oligoarticular (16%), Polyarticular (64%; 20% were rheumatoid factor positive), and Systemic (20%). At study entry, 74% of patients were receiving MTX (mean dose, 13.2 mg/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.

Clinical Response

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

During the double-blind randomized withdrawal phase (Period B), ORENCIA-treated patients experienced significantly fewer disease flares compared to placebo-treated patients (20% vs 53%); 95% CI of the difference (15%, 52%). The risk of disease flare among patients continuing on ORENCIA was less than one third than that for patients withdrawn from ORENCIA treatment (hazard ratio=0.31, 95% CI [0.16, 0.59]).

Among patients who had a clinical response at the end of Period A and entered into Period B, the majority of those patients remaining on ORENCIA continued to improve from month 4 to month 10. Most patients who experienced a disease flare in Period B, and re-introduced ORENCIA treatment up to six months after discontinuation re-responded to ORENCIA in Period C, the open-label extension.

In general, the patients who continuously received ORENCIA during both Period B and during the first three months of the open-label extension Period C maintained their responses, although no formal efficacy conclusions can be drawn from Period C.

Adult Psoriatic Arthritis:

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

In PsA-I, 424 patients were randomized 1:1 to receive weekly doses of SC placebo or ORENCIA 125 mg without a loading dose for 24 weeks-in a double-blind manner, followed by open-label ORENCIA 125 mg SC weekly. Randomization was stratified by current MTX use, prior use of TNFi therapy, and the percentage of psoriasis-affected body surface area ($\geq 3\%$ vs $< 3\%$). Patients were allowed to receive stable doses of concomitant methotrexate, sulfasalazine, leflunomide, hydroxychloroquine, low dose corticosteroids (equivalent to ≤ 10 mg of prednisone) and/or NSAIDs during the trial. At randomization, 60.4% of patients were receiving methotrexate. At baseline, the mean weight for subjects randomized to abatacept was 84.9 kg and to placebo was 86.6 kg, with a limited number of subjects weighing < 60 kg (16 subjects and 15 subjects, respectively). The baseline disease characteristics included presence of joint erosion on X-rays in 84% (341/424) 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% [277/424] with a mean (SD) of 14.1 mg/L (25.9), and polyarticular disease in 98% (416/424) of patients with a mean number (SD) of tender joints and swollen joints of 20.2 (13.3) and 11.6 (7.5), respectively. Patients who had not achieved at least a 20% improvement from baseline in their swollen and tender joint counts by Week 16 escaped to open-label ORENCIA 125 mg SC weekly.

In PsA-II, an IV dose-ranging study, 170 patients received study drug at Day 1, 15, 29, and then every 28 days thereafter in a double blind manner for 24 weeks, followed by open-label ORENCIA 10 mg/kg IV every 28 days. Patients were randomized to receive placebo or ORENCIA 3 mg/kg (3/3), 10 mg/kg (10/10), or two doses of 30 mg/kg followed by 10 mg/kg (30/10) without escape for 24 weeks. The randomization

was stratified by the percentage of psoriasis-affected body surface area ($\geq 3\%$ vs $< 3\%$). Patients were allowed to receive stable doses of concomitant methotrexate, low dose corticosteroids (equivalent to ≤ 10 mg of prednisone) and/or NSAIDs during the trial. At enrollment, approximately 60% of patients were receiving methotrexate. 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) or 10.9 (7.6), respectively.

In PsA-I, 69.0% (147/213) of subjects in the abatacept group and 69.2% (146 /211) of subjects in the placebo group received concomitant non-biologic DMARDs during the double-blind period. In PsA-II, 60.0% (24/37) of subjects in the abatacept group and 54.8% (23/35) of subjects in the placebo group received concomitant non-biologic DMARDs during the double-blind period.

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

A significantly higher proportion of patients achieved an ACR20 response after treatment with ORENCIA 10 mg/kg IV or 125 mg SC compared to placebo at Week 24. The percent of patients achieving ACR 20, 50, or 70 responses in Studies PsA-I and PsA-II (10 mg/kg) are presented in Table 21 below.

Table 21: Proportion of Patients With ACR Responses at Week 24 in Studies PsA-I^a and PsA-II

	PsA-I ^b		PsA-II ^c	
	ORENCIA 125 mg SC N=213	Placebo N=211	ORENCIA 10mg/kg IV ^b N=40	Placebo N=42
ACR 20	39.4%*	22.3%	47.5%	19.0%
Estimate of Difference (95% CI)		17.2% (8.7%, 25.6%)		28.7% (9.4%, 48.0%)
p-value		< 0.001 ^d		0.006 ^e
ACR 50	19.2%	12.3%	25.0%	2.4%
ACR 70	10.3%	6.6%	12.5%	0%

^a Patients who had less than 20% improvement in tender or swollen joint counts at Week 16 met escape criteria [76 (35.7%) in abatacept and 89 (42.2%) in placebo] and were considered non-responders.

^b 61% of patients were previously treated with tumor necrosis factor inhibitor (TNFi).

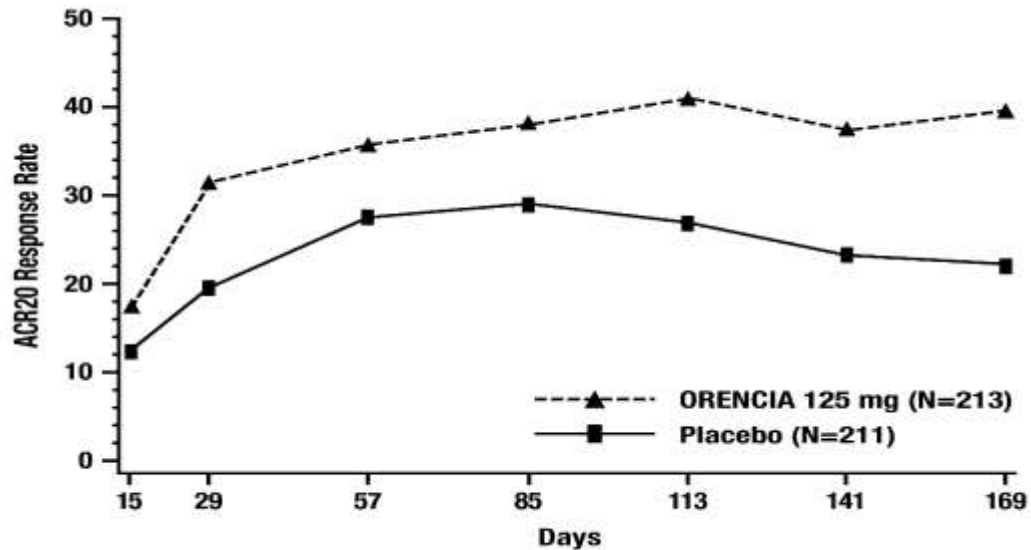
^c 37% of patients were previously treated with TNFi.

^d p-value is based on the CMH Chi-square test stratified by MTX use, prior TNFi and BSA. Estimate and 95% CI for difference are based on stratum size weights method stratified by MTX use, prior TNFi and baseline BSA.

^e p-value is based on the CMH Chi-square test stratified by BSA. Estimate and 95% CI for difference are based on stratum size weights method stratified by baseline BSA.

The percentage of patients in PsA-I achieving ACR20 response through Week 24 is shown below in Figure 6.

Figure 6: Percent of Patients Achieving ACR20 Response^a in PsA-I Study Through Week 24 (Day 169)



^aNon-responder imputation for early escape subjects at Day 141 and 169

ACR 20 responses at Week 24 were higher in the abatacept group compared to the placebo group regardless of prior TNFi treatment and concomitant non-biologic DMARD use. The proportion of subjects who met the ACR 20 criteria for responders at Week 24 was 44.0% in the abatacept group and 22.2% in the placebo group in TNFi-naive subjects, and 36.4% in the abatacept group and 22.3% in the placebo group in TNFi-exposed subjects. The proportion of subjects who met the ACR 20 criteria for responders at Week 24 was 44.9% in the abatacept group and 26.9% in the placebo group for those using concomitant non-biologic DMARD, and 27.3% in the abatacept group and 12.1% in the placebo group for those not using concomitant non-biologic DMARDs.

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

In PsA-I, 65.7% (140/213) of subjects in the abatacept group and 62.6% (132/211) of subjects in the placebo group had enthesitis at baseline. Dactylitis occurred in 28.6% (61/213) of subjects in the abatacept group and in 23.7% (50/211) of subjects in the placebo group at baseline. In PsA-I, among subjects with dactylic digits at baseline, the proportion of subjects with no dactylic digits at Week 24 was 44.3% in the abatacept group and 34.0% in the placebo group. Among subjects with enthesitis at baseline, the proportion of subjects with no enthesitis at Week 24 was 32.9% in the abatacept group and 21.2% in the placebo group.

Radiographic Response

In study PsA-I, the proportion of radiographic non-progressors (≤ 0 change from baseline) in total PsA-Modified SHS at Week 24 was 42.7% in the ORENCIA 125 mg group compared to 32.7% in the placebo group.

Physical Function Response

In study PsA-I, at Week 24, the proportion of patients with at least ≥ 0.35 decrease from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) was 31.0% on ORENCIA compared to 23.7% on placebo. The adjusted mean change from baseline in HAQ-DI was -0.33 on ORENCIA compared to -0.20 on placebo. In study PsA-II, at Week 24, the proportion of patients with at least ≥ 0.30 decrease from

baseline in HAQ-DI score was 45.0% with ORENCIA 10 mg/kg compared to 19.0% on placebo.

Prophylaxis of Acute Graft versus Host Disease after Unrelated-donor HSCT

The efficacy of ORENCIA, when added to a standard of care regimen of a calcineurin inhibitor (CNI) (cyclosporine or tacrolimus) and methotrexate (MTX) for prophylaxis of acute graft versus host disease (aGVHD), was assessed in Study GVHD-1, a study of hematopoietic stem cell transplant (HSCT) recipients and Study GVHD-2, a clinical study that used data from the Center for International Blood and Marrow Transplant Research (CIBMTR).

In Study GVHD-1, ORENCIA was administered at a dose of 10 mg/kg IV (1000 mg maximum dose) as intravenous infusion over 60 minutes, beginning on the day prior to transplantation (Day -1), followed by administration on 5, 14, and 28 days after the transplantation. Two cohorts of patients were studied:

- A randomized (1:1), double-blind, placebo-controlled study of patients who underwent an 8 of 8 HLA-matched HSCT who received ORENCIA (73 patients) or placebo (69 patients) in combination with a CNI and MTX (8 of 8 cohort); and
- An open-label, single-arm study of 43 patients who underwent a 7 of 8 Human Leukocyte Antigen (HLA)-matched HSCT (7 of 8 cohort).

Baseline demographic and clinical characteristics of both the 7 of 8 and 8 of 8 cohorts are outlined below in **Error! Reference source not found.**

Table 22: Baseline Demographic and Clinical Characteristics: 7 of 8 and 8 of 8 Cohort Treated Analysis Population in Study GVHD-1.

	7 of 8 Cohort	8 of 8 Cohort	
	ORENCIA (+ CNI and MTX)	ORENCIA (+ CNI and MTX)	Placebo (+CNI and MTX)
	N=43	N=73	N=69
Age - Median	38	44	40
Age - Range	6-76	6-71	7-74
Gender - Male	27 (63)	41 (56)	37 (54)
White	31 (72)	63 (86)	61 (88)
Black or African American	7 (16)	3 (4.1)	2 (2.9)
Asian	2 (4.7)	4 (6)	2 (2.9)
Hispanic	7 (16)	4 (6)	2 (2.9)
Malignancy type			
Acute Myeloid Leukemia (AML)	15 (35)	30 (41)	22 (32)
Myelodysplastic Syndrome (MDS)	11 (26)	15 (21)	12 (17)
Acute Lymphoblastic Leukemia (ALL)	8 (19)	20 (27)	22 (32)
Acute leukemia of ambiguous lineage	1 (2.3)	0	1 (1.4)
Hodgkin and Non-Hodgkin lymphoma	1 (2.3)	1 (1.4)	1 (1.4)
Acute Lymphoblastic Lymphoma in 2nd or Greater Complete Remission	1 (2.3)	4 (6)	1 (1.4)
Chronic Myelomonocytic leukemia	1 (2.3)	1 (1.4)	4 (6)
Chronic Myelogenous leukemia	4 (9)	1 (1.4)	5 (7)
Not reported	1 (2.3)	1 (1.4)	1 (1.4)
GVHD Prophylaxis			
Cyclosporine	16 (37)	11 (15)	11 (16)
Tacrolimus	27 (63)	62 (85)	58 (84)
Type of Graft			
Bone Marrow	21 (49)	33 (45)	26 (38)
Cytokine Mobilized Peripheral Blood (PBSC)	22 (51)	40 (55)	43 (62)
Conditioning Regimen			
TBI and Chemotherapy	11 (26)	20 (27)	26 (38)
Busulfan and Cyclophosphamide	13 (30)	28 (38)	21 (30)
Busulfan and Fludarabine	8 (19)	7 (10)	2 (2.9)
Melphalan and Fludarabine	11 (26)	18 (25)	20 (29)

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

Clinical Response: 8/8 Cohorts

Efficacy in Study GVHD-1 was established based on overall survival (OS) and grade II-IV aGVHD free survival (GFS) results assessed at Day 180 post-transplantation. ORENCIA +CNI and MTX did not significantly improve grade III-IV GFS versus placebo + CNI and MTX at Day 180 post-transplantation. The efficacy results of the GVHD-1 8 of 8 cohort are shown in [Error! Reference source not found.](#)

Table 23: Efficacy Results in 8 of 8 Cohort in Study GVHD-1 at Day 180 Post-Transplantation

Endpoint	ORENCIA (+CNI and MTX) n=73	Placebo (+CNI and MTX) n=69
Gr III-IV aGVHD Free Survival ^a Rate (95% CI)	87% (77%, 93%)	75% (63%, 84%)
Hazard Ratio (95% CI)	0.55 (0.26, 1.18)	
Gr II-IV aGVHD Free Survival ^b Rate (95% CI)	50% (38%, 61%)	32% (21%, 43%)
Hazard Ratio (95% CI)	0.54 (0.35, 0.83)	
Overall Survival Rate (95% CI)	97% (89%, 99%)	84% (73%, 91%)
Hazard Ratio (95% CI)	0.33 (0.12, 0.93)	

^a Gr III-IV aGVHD Free Survival was measured from the date of transplantation until the onset of documented Grade III-IV aGVHD, or death by any cause up to Day 180 post-transplantation.

^b Gr II-IV aGVHD Free Survival was measured from the date of transplantation until the onset of documented Grade II-IV aGVHD, or death by any cause up to Day 180 post-transplantation.

Clinical Response: 7/8 Cohorts

In Study GVHD-2, the OS rate at Day 180 in the ORENCIA in combination with CN1 and MTX group was 98% (95% CI: 78, 100) and the OS rate at Day 180 in the CN1 and MTX group was 75% (95%CI: 67, 82) for patients who underwent HSCT from a 1 allele-mismatched URD. In Study GVHD-1, exploratory analyses found a similar trend to those in GVHD-2.

14.3 Immunogenicity

Adult RA Patients Treated with Intravenous Orencia

In studies AIM, ATTAIN, ASSURE, IM101100, IM101101, patients with rheumatoid arthritis were tested for antibodies to ORENCIA at multiple time points. Antibodies to the entire abatacept molecule or to the CTLA-4 portion of abatacept were measured. Binding antibodies were detected in 2.8% of 2237 patients tested over a period of up to 3 years. No apparent correlation of antibody development to clinical response or adverse events was observed, but due to the small number of patients across studies who developed an immune response, conclusions concerning the impact of immunogenicity on safety and efficacy cannot be made.

Adult RA Patients Treated with SC ORENCIA

All patients received an IV abatacept loading dose by weight on Day 1. In the SC abatacept group, 0.4% and 0.7% of patients were positive for anti-abatacept and anti-CTLA4-T antibodies, respectively, vs. 0.7% and 1.5% respectively in the IV abatacept group; 714/736 and 725/736 patients treated with intravenous abatacept and 698/721 and 710/721 patients treated with SC abatacept were tested for anti-abatacept and anti-CTLA4-T antibodies respectively. During 6 months of treatment, injection site reactions, hypersensitivity reactions or autoimmune disorders did not occur in any sero-positive patients.

SC ORENCIA Administration without an IV Loading Dose

A study in the subcutaneous program was conducted to determine the effect of monotherapy use of ORENCIA on immunogenicity following subcutaneous administration without an intravenous loading dose (IM101-173). The results indicated that there were no differences in the frequency of immunogenicity after 4 months of treatment when ORENCIA was administered as a monotherapy or in combination with methotrexate (immunogenicity was not detected in either group at Month 4: n=49, ORENCIA; n=51, ORENCIA plus MTX) (see [4 DOSAGE AND ADMINISTRATION](#) and [10 CLINICAL PHARMACOLOGY](#)).

SC ORENCIA upon Withdrawal (Three Months) and Restart of Treatment

A study (IM101-167) in the subcutaneous program was conducted to investigate the effect of withdrawal (three months) and restart of ORENCIA subcutaneous treatment on immunogenicity. Upon withdrawal of ORENCIA subcutaneous treatment, the increased rate of immunogenicity was consistent with that seen upon discontinuation of ORENCIA administered intravenously. Upon reinitiating therapy, there were no injection reactions and no differences in response to therapy in patients who were withdrawn from subcutaneous therapy for up to 3 months relative to those who remained on subcutaneous therapy, whether therapy was reintroduced with or without an intravenous loading dose (see [4 DOSAGE AND ADMINISTRATION](#) and [10 CLINICAL PHARMACOLOGY](#)).

JIA/JRA Patients 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 JIA/JRA patients following repeated treatment with ORENCIA throughout the open-label period. For patients who were withdrawn from therapy for up to 6 months during the double-blind period, the rate of antibody formation to the CTLA-4 portion of the molecule was 40.7% (22/54), while for those who remained on therapy the rate was 13.0% (7/54).

The long-term immunogenicity of ORENCIA is unknown.

Prophylaxis of Acute Graft versus Host Disease after Unrelated-donor HSCT

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

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

The nonclinical safety profile of abatacept was evaluated in mice, rats, and cynomolgus monkeys. Pharmacologic activity has been demonstrated in each of these species. Abatacept, a fully human protein, was immunogenic in each of these species; however, abatacept-specific antibodies were generally detected only during the recovery period, indicating that abatacept-specific antibodies were not formed until after abatacept serum levels had dropped below pharmacologically active levels.

General Toxicology:

Single and Repeat-Dose Toxicity

In non-human primate studies, significant drug-related toxicity did not occur following the intravenous infusion of abatacept 1) as a single dose of up to 100 mg/kg or 2) as repeat doses of up to 50 mg/kg every other day for 30 days or every week for 1 year. Reversible pharmacologic effects in the repeat-dose studies consisted of minimal decreases in serum immunoglobulin (Ig) G and mild to moderate decreases in the number and diameter of lymphoid germinal centers in the spleen and/or lymph nodes (1-year study), morphologic features reflective of decreased germinal center activity. In repeat-dose studies, no hyperplastic, preneoplastic, or neoplastic changes were observed in the peripheral blood cells or lymphoid tissues of any monkey. In the 1-year study, functional activity of the immune system was demonstrated at all doses by a robust antibody response to the T-cell-dependent antigen keyhole limpet hemocyanin following immunization after an 8-week dose-free period. Abatacept treatment for 1 year did not result in any clinical manifestations representative of a viral infection or sequelae, even though viral screening confirmed previous exposure in all monkeys to one or more of the following viruses:

lymphocryptovirus, herpes B, rhesus cytomegalovirus, or simian papovavirus. The no-observable-adverse-effect level (NOAEL) in the 1-year study was 50 mg/kg/weekly, which resulted in a systemic exposure, based on area under the concentration versus time curves (AUCs), that was 9-fold greater than human exposure at the clinical dose.

No significant toxicity was observed in rats at doses up to 200 mg/kg, administered either intravenously or subcutaneously every 2 days for a total of seven doses (q2dx7). A minimal decrease in serum IgG and IgA was noted at the completion of treatment. Bioavailability following subcutaneous administration was between 41% (200 mg/kg) and 63% (10 mg/kg).

In mice, subcutaneous administration of abatacept once weekly for 26 weeks at doses up to 200 mg/kg was clinically well tolerated. At doses of ≥ 65 mg/kg, reversible, pharmacologic effects consisted of transient decreases in mean serum IgG levels and, in male mice, decreases in the percentages of splenic B cells and inhibition of ex vivo B- and T-cell activation. Increases in the incidence and severity of karyomegaly in renal tubular epithelial cells that was accompanied by mild, multifocal, chronic inflammation, lymphocytic infiltration, and tubular cell degeneration were observed at ≥ 65 mg/kg. This renal finding did not have any untoward effects on renal function and was interpreted as an exacerbation of a spontaneous, age-related renal change that occur in mice but has no known relevance to humans. The NOAEL for this study was considered to be 200 mg/kg (human exposure multiple of 4.7).

Mutagenicity and Carcinogenicity: No mutagenic potential of abatacept was observed in the in vitro reverse Ames or Chinese hamster ovary/hypoxanthine guanine phosphoribosyl-transferase (CHO/HGPRT) forward point mutation (with or without metabolic activation) assays. No chromosomal aberrations were observed in human lymphocytes (with or without metabolic activation) treated with abatacept. In a mouse carcinogenicity study, weekly subcutaneous injections of 20, 65, or 200 mg/kg of abatacept administered each week 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 were 0.8-, 2.0- and 3.0-fold, the human exposure at 10 mg/kg, respectively, based on AUC. No evidence of lymphomas or preneoplastic morphologic changes was observed in the 1-year monkey study, 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 abatacept is unknown.

Reproductive and Developmental Toxicology: In a fertility and early embryonic development study in rats, there were no effects on mating, fertility, or early embryonic development at doses up to 200 mg/kg administered intravenously every 3 days (human exposure multiple of 11). In the intravenous embryo-fetal development studies, no adverse effects were detected in rodents at doses up to 200 mg/kg (rats) or 300 mg/kg (mice) administered daily or in rabbits at doses up to 200 mg/kg administered every 3 days (human exposure multiple of 30- and 29-fold for rats and rabbits). In the rat and rabbit studies, abatacept was shown to cross the placenta. In the pre- and post-natal development study in rats, there were no effects on the F0-generation dams at doses up to 200 mg/kg (human exposure multiple of 11) administered intravenously every 3 days and no effects on the F1-generation rats at ≤ 45 mg/kg (human exposure multiple of 3). At 200 mg/kg, drug-related changes in the F1-generation were limited to females

and consisted of a 9-fold increase in the T-cell-dependent antibody response and inflammation of the thyroid of 1 rat. These findings, of unknown relevance to humans, occurred at 11-fold human exposures; no effects were noted at 3-fold the human exposure. No other immune parameters were affected (splenic-lymphocyte and natural-killer cell phenotypes, serum Ig levels, and presence of anti-nuclear antibodies).

Local Tolerance: Abatacept was not significantly irritating when administered to rabbits by intravenous, paravenous, or intra-arterial injection at concentrations expected to be the highest concentration intended for use in humans (10 mg/mL). In intravenous repeat-dose studies in monkeys, no significant injection site irritation occurred at concentrations (25-31 mg/mL) well above the concentrations recommended for human use. In the subcutaneous repeat-dose studies in mice and the single- and repeat-dose studies in rats, no significant injection site irritation occurred at concentrations up to 100 mg/mL.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrORENCIA®

(or EN see ah)

abatacept for injection, intravenous infusion, 250 mg / vial

PrORENCIA®

abatacept injection, solution for subcutaneous injection, 125 mg / mL

Read this carefully before you start taking **ORENCIA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ORENCIA**.

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 condition.

Serious Warnings and Precautions

- **Serious infections:** There have been some cases where patients receiving **ORENCIA**, or other RA biologic treatment, have developed serious infections, including tuberculosis (TB) and infections caused by viruses, bacteria, or fungi.
- **Allergic reactions:** If you develop a severe rash, chest pain, swollen face or difficulty breathing during or after receiving **ORENCIA**, call your doctor immediately. The prefilled syringe components do not contain any latex or dry natural rubber.

What is **ORENCIA** used for?

- Adults with moderate to severe rheumatoid arthritis (RA). RA is a disease that causes pain and joint inflammation (tenderness and swelling). RA can also cause joint damage. Your doctor has decided to treat you with **ORENCIA** because your disease is still active even though you have tried other treatments.
- Children and adolescents with moderately to severely active juvenile idiopathic arthritis (JIA)/juvenile rheumatoid arthritis (JRA) with polyarticular course after one or more JIA/JRA medicines have been used and not worked.
- Adults with active psoriatic arthritis (PsA) who failed to respond to other PsA treatments. In adults, **ORENCIA** can be used alone or with other PsA treatments.
- Adults and children 6 years of age and older undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated-donor for prophylaxis of moderate to severe acute graft versus host disease (aGVHD).

ORENCIA is supplied in vials for intravenous (IV) infusions (given through a needle placed in your arm vein), and in prefilled syringes for subcutaneous (SC) injections [given just under the skin of your abdomen (tummy), arms or legs] with the active ingredient called “abatacept”.

- The **ORENCIA** SC Injection syringe cannot be used for IV infusion.

- The ORENCIA vial for IV Infusion cannot be used for SC injections.

How does ORENCIA work?

ORENCIA is a medicine that keeps the immune system from attacking healthy tissues in the body. The immune system is the body's defense against attack, such as infections by bacteria and viruses. A normal immune system leaves healthy body tissues alone.

In people with RA, PsA, or aGVHD, the immune system attacks normal body tissues. This can cause damage and inflammation especially in the tissues of your joints. PsA may be accompanied by psoriasis. Psoriasis is an inflammatory disease that affects the skin and can cause raised, thick, red and scaly patches ("psoriatic skin lesions") that can appear anywhere on the body. Psoriatic arthritis is usually seen in patients with psoriasis and affects both the joints and the skin.

Acute graft versus host disease (aGVHD) is a systemic disorder mediated by donor lymphocytes when infused into the recipient, encounter tissue damages exaggerated from the effects of the underlying disease, prior infections, and the transplant conditioning regimen. This immune-mediated cytotoxic response is determined by severity, varying from mild to very severe affecting alone or in combination with the skin, liver or gastrointestinal (GI) tract. aGVHD occurs mainly in patients undergoing allogeneic hematopoietic stem cell transplant.

ORENCIA modifies an important step in this attack. By decreasing the immune system's attack on normal tissues, ORENCIA can reduce pain, joint inflammation, and damage to your bones and cartilage. ORENCIA may also help you with your daily activities (such as getting dressed, walking and climbing stairs).

However, ORENCIA also can lower your body's ability to fight infection. ORENCIA treatment can make you more prone to getting infections or make any infection you have worse. It is important to tell your doctor if you think you have any infections, like a cold, flu, infected cuts, etc.

No data for children <6 years of age are available to Health Canada, therefore, Health Canada has not authorized an indication for pediatric use <6 years.

What are the ingredients in ORENCIA?

Medicinal ingredients: abatacept

What the Non-medicinal ingredients are:

- Intravenous formulation: Maltose, sodium chloride and sodium phosphate.
- Subcutaneous formulation: Sucrose, poloxamer 188, monobasic sodium phosphate monohydrate, dibasic sodium phosphate anhydrous, water for injection.

ORENCIA comes in the following dosage forms:

250 mg / vial for IV use and 125 mg / mL single-dose disposable prefilled syringes for SC administration.

Do not use ORENCIA if:

- you have ever had an allergic reaction to ORENCIA
- you have an infection that has spread through your body (sepsis)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ORENCIA. Talk about any health conditions or problems you may have, including if you:

- Have any kind of infection including an infection that is in only one place in your body (such as an open cut or sore), or an infection that is in your whole body (such as the flu). Having an infection could put you at risk for serious side effects from ORENCIA. If you are not sure, please ask your doctor.
- For patients undergoing transplant prior to the procedure your healthcare provider may want to know whether you have an inactive infection with cytomegalovirus (CMV) or Epstein-Barr Virus (EBV). Prior infection with CMV or EBV, which is very common, may have an impact on the risk of developing reinfection with either of these viruses. Your healthcare provider may give you antiviral medicines before, during, and after your transplantation to help prevent EBV and CMV infections. If you are experiencing flu-like symptoms i.e. fever, chills, fatigue, muscle aches, decreased appetite, rash or swollen lymph nodes inform your doctor for further examination.
- Have an infection that won't go away or a history of infections that keep coming back.
- Have had tuberculosis (TB), or if you recently have been in close contact with someone who has had TB. If you develop any of the symptoms of TB (a dry cough that doesn't go away, weight loss, fever, night sweats) call your doctor right away. Before you start ORENCIA, your doctor may examine you for TB or perform a skin test.
- Have or have had viral hepatitis. Before you use ORENCIA your doctor may examine you for hepatitis.
- Have diabetes and are using a blood glucose monitor to check your blood glucose levels. ORENCIA for intravenous infusion (given through a needle placed in a vein) contains maltose, which is a type of sugar that can give falsely high blood glucose readings with certain types of blood glucose monitors on the day of ORENCIA infusion. Your doctor may recommend a different method for monitoring your blood glucose levels. ORENCIA for subcutaneous administration (injected under the skin) does not contain maltose; therefore, you do not need to change your glucose monitoring.
- Are scheduled to have surgery.
- Recently received a vaccination or are scheduled for any vaccination. Some vaccines should not be given while you are receiving ORENCIA. If your child is to receive ORENCIA, discuss your child's vaccination history and plans with your doctor. All vaccines should be brought up-to-date before starting ORENCIA and patients taking ORENCIA should not receive live vaccines.
- Have a history of chronic obstructive pulmonary (lung) disease (COPD).
- Are pregnant or are planning to become pregnant. If you took ORENCIA during pregnancy, talk to your doctor before your baby receives any vaccines.
- Are breastfeeding.

If you are not sure or have any questions about any of this information, ask your doctor.

Other warnings you should know about:

Malignancies: During the clinical trials, certain kinds of cancer have been reported in patients treated with ORENCIA, these case reports are regarded as uncommon. Lung cancer and cancer of the lymph

glands were reported more often in patients treated with ORENCIA than in patients treated with placebo. The current number of reported cancer cases in the ORENCIA studies appears to be consistent with the expected number of cancer cases reported in the RA population. People with more serious RA that have had the disease for a long time may have a higher than average risk of getting a kind of cancer that affects the lymph system, called lymphoma. If you take ORENCIA or other RA biologic treatment, your risk may increase. The role of ORENCIA in the development of cancer is not known.

There have been reports of certain kinds of skin cancer in patients taking ORENCIA. Some patients receiving ORENCIA have developed types of cancer called non-melanoma skin cancer. If any changes in the healing or the appearance of your skin or growths on your skin occur during or after your treatment with ORENCIA, tell your doctor.

ORENCIA has not been studied in pregnant women or nursing mothers, so we don't know what the effects are on pregnant women or nursing babies. You should tell your doctor if you are pregnant, or are planning to become pregnant. If you took ORENCIA during pregnancy, talk to your doctor before your baby receives any vaccines.

You can take other medicines with ORENCIA if your doctor has prescribed them or has told you it is okay to take them while you are receiving ORENCIA. It is important to tell your doctor if you are taking any other medicines including hormones, over the counter medicines, vitamins, supplements, or herbal products before you are treated with ORENCIA. If you start taking or plan to start taking any new medicine while you are receiving ORENCIA, tell your doctor.

ORENCIA should not be taken with other biologic medications for RA such as Enbrel[®], Humira[®], Remicade[®], or Kineret[®].

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ORENCIA:

- No special studies were done to look at whether ORENCIA interferes with blood levels of common RA medications; nor were they done to look at whether common RA medications interfere with blood levels of ORENCIA. Information from clinical studies so far have not suggested a problem like this.
- ORENCIA should not be taken with other biologic medications for RA such as Enbrel[®], Humira[®], Remicade[®], or Kineret[®].

How to take ORENCIA:

ORENCIA may be administered as an intravenous infusion (IV) or a subcutaneous (SC) injection.

Intravenous Infusion

- ORENCIA will be given to you by a healthcare professional using an IV. This is called an infusion. This means the medicine will be given to you through a needle placed in a vein in your arm. It will take about 30 minutes (60 minutes for aGVHD prophylaxis) to give you the full dose of medicine.
- You will receive your first dose of ORENCIA followed by additional doses at 2 and 4 weeks after the first dose. You will then receive a dose every 4 weeks.

Subcutaneous injection

- ORENCIA, as a subcutaneous injection (injected under the skin), is administered every week.
- If you have rheumatoid arthritis, you may start with one IV dose (see above) then you will get weekly SC injections.
- Your first SC dose should be given by your healthcare provider. If your healthcare provider decides that you or a caregiver may be able to give your injections of ORENCIA at home, you should receive training on the right way to prepare and inject ORENCIA. Do not try to inject ORENCIA yourself until you have been shown the right way to give the injections by your healthcare provider. ORENCIA for subcutaneous injection should be injected one time each week.
- See the detailed Patient/Caregiver Instructions for use instructions about the right way to prepare and administer your ORENCIA subcutaneous injections at home.

Usual dose:

INTRAVENOUS INFUSION

Adults with RA/PsA

Depending on how much you weigh, you will receive 2 - 4 vials of ORENCIA at a time.

Body Weight of Patient	Dose	Number of Vials ^a
< 60 kg (132 lbs)	500 mg	2
60 to 100 kg (132 - 220 lbs)	750 mg	3
> 100 kg (220 lbs)	1 gram	4

^a Each vial provides 250 mg of abatacept for administration.

Children above 6 years of age (JIA/JRA)

The dose for children who weigh less than 75 kg will be determined by the child's weight. The dose for children weighing 75 kg or more will be determined as outlined above for adults.

Adults and Children above 6 years of age for the prophylaxis of aGVHD

Orencia is administered at a 10 mg/kg dose (maximum dose of 1000 mg) as a 60-minute intravenous infusion. The initial dose should be administered on the day before transplantation (Day -1), followed by a dose on Day 5, 14, and 28 after transplant.

SUBCUTANEOUS ADMINISTRATION

Adults

If your first dose of ORENCIA is given IV (through a needle placed in your arm), it will be administered according to your weight then your next doses will be given as an injection under the skin of your abdomen (tummy), arms or legs.

ORENCIA subcutaneous injection (injected under the skin) is administered one time each week as a 125 mg injection (full amount contained in the syringe) regardless of how much you weigh. (See

“Patient/Caregiver Instructions” for details.)

Overdose:

If you think you, or a person you are caring for, have taken too much ORENCIA, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss your appointment or if you forget to receive your ORENCIA injection, ask your doctor when to schedule your next dose or take your next subcutaneous injection.

What are possible side effects from using ORENCIA?

These are not all the possible side effects you may have when taking ORENCIA. If you experience any side effects not listed here, tell your healthcare professional.

Like all medicines that affect your immune system, ORENCIA can cause side effects, some of which may be serious.

The more common side effects with ORENCIA are headache, upper respiratory tract infection, sore throat, and nausea. Infusion related reactions were infrequent during the clinical studies with ORENCIA.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON [happens to 1 in every 100 to 1000 patients (less than 1%)]			
Pneumonia (lung infection)		√	
Cellulitis (skin infection)		√	
Urinary tract infection		√	
Bronchitis (lung infection)		√	
Diverticulitis (infection of large intestine)		√	
Pyelonephritis (kidney infection)		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage

Your ORENCIA intravenous vials should be stored under refrigeration (2°C - 8°C) and protected from light. Your healthcare professional will prepare the solution for intravenous (IV) infusion.

Your ORENCIA subcutaneous syringes should be stored under refrigeration (2°C-8°C) and protected from light. Do not allow the prefilled syringe to freeze and do not use beyond the expiration date on the syringe. If frozen, do not use.

If you want more information about ORENCIA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website www.bms.com/ca/en, or by calling the sponsor, Bristol-Myers Squibb Canada at 1-866-463-6267.

This leaflet was prepared by Bristol-Myers Squibb Canada.

Last Revised: MAY 19, 2023

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**PATIENT/CAREGIVER INSTRUCTIONS FOR USE -
ORENCIA ABATACEPT INJECTION
PREFILLED SYRINGE WITH BD ULTRASAFE
PASSIVE™ NEEDLE GUARD WITH FLANGE
EXTENDERS**

Getting started with ORENCIA therapy

Did you receive self-injection training from a healthcare professional?

Your doctor or nurse should arrange for in-person training to familiarize you and/or your caregiver with the use of your prefilled syringe.

Keep away from children and pets.

**Your ORENCIA prefilled syringe with
BD UltraSafe Passive™ Needle Guard with
Flange Extenders overview**

**DO NOT REMOVE THE NEEDLE COVER
(THE CAP) UNTIL YOU ARE READY TO
INJECT**

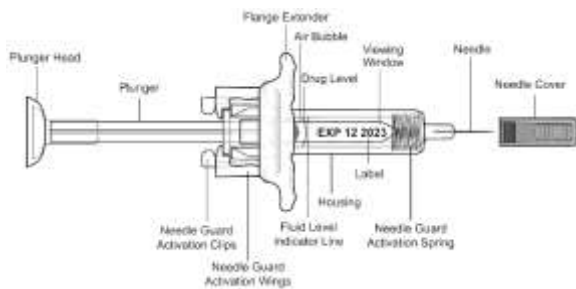


Figure 1

- The ORENCIA prefilled syringe is designed for easy use by you or your caregiver. It has a flange extender that makes it easier to hold the syringe and inject and a needle guard that automatically extends over the needle after the injection is complete (see Figure 1).
- Always handle the syringe carefully, especially when you are around other people, children and animals.

Before you use the ORENCIA prefilled syringe with BD UltraSafe Passive™ Needle Guard with Flange Extenders

Do

- Always hold the syringe by the body of the syringe.
- Remove the syringe from the refrigerator 30 to 60 minutes prior to injecting.
- Check the expiration date on the carton and syringe (see Figure 1). Do not use if expired.
- Store unused syringes in the refrigerator in the original carton.
- Have your additional injection supplies ready prior to injection.
 - Supplies checklist: Alcohol swab, cotton ball or gauze, adhesive bandage and Sharps container (see Figure 2).

Don't

- Do not remove the needle cover until you are ready to inject.
- Do not pull back on the plunger at any time.
- Do not shake the ORENCIA syringe, as this may damage the medicine.
- DO NOT FREEZE. If product has been frozen, do not use.



Figure 2

STEP 1: Get your syringe ready

- A. Check the expiration date
- The expiration date can be found on the ORENCIA carton and on each syringe.

- If the expiration date has passed, do not use the prefilled syringe. Please contact your doctor or pharmacist for assistance.

B. Let it warm up for 30 to 60 minutes

- Find a comfortable space with a clean, flat working surface.
- Remove the syringe from the refrigerator. Keep remaining unused syringes in their original carton and keep in refrigerator. **DO NOT FREEZE.**
- Inspect the syringe for obvious flaws, **but do not remove needle cover.**
- Allow the syringe to rest at room temperature for at least 30 to 60 minutes prior to injection. This may allow for a more comfortable injection experience.
 - **Do not** speed the warming process in any way, such as using the microwave or placing the syringe in warm water.

C. Check the liquid in the prefilled syringe

- Hold your ORENCIA prefilled syringe by the housing with the covered needle pointing down (see Figure 3).

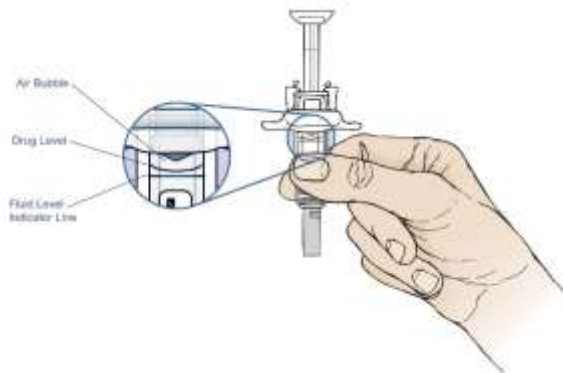


Figure 3

- Look at the liquid through the viewing window of your prefilled syringe. The liquid in your syringe should be clear to pale yellow. Do not inject if the liquid is cloudy, discolored or has large particles.
- Confirm the drug level is above the fluid indicator level (see Figure 3). Do not inject

if the drug level is outside of the fluid level indicator lines. It is normal to see an air bubble and there is no reason to remove it.

D. Gather your additional supplies and keep them within easy reach.

E. Wash your hands thoroughly with soap and warm water.

STEP 2: Choose and prepare a section on your body for the injection (injection site)

Have your ORENCIA prefilled syringe with BD UltraSafe Passive™ Needle Guard with Flange Extenders ready for use immediately after preparing the injection site.

A. Choose your injection site

- The front of your thigh is a recommended injection area. You may use your abdomen except for the 2-inch area around the navel (see Figure 4).
- The outer area of the upper arms may also be used only if the injection is being given by a caregiver. Do not attempt to use the upper arm area by yourself (see Figure 5).
- Choose a different injection site for each new injection. You may use the same thigh for weekly injections, as long as each injection is approximately 1 inch apart from the last time you injected yourself in that area.
- Do not inject into areas where your skin is tender, bruised, red, scaly, or hard. Avoid any areas with scars or stretch marks.

Areas appropriate for self-injection and caregiver injection

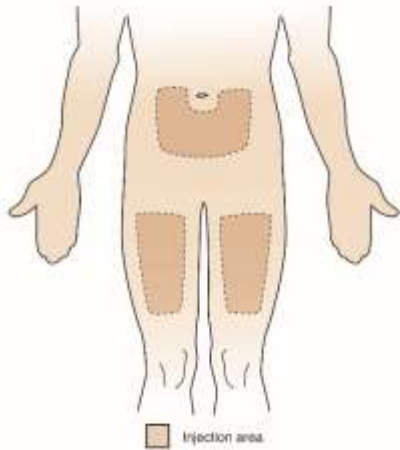


Figure 4

Additional injection area option for caregivers only

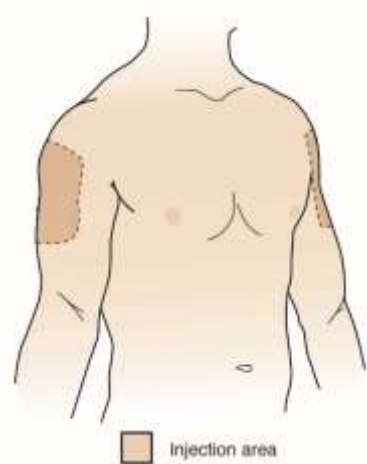


Figure 5

B. Prepare your injection site

- Wipe the injection site with an alcohol swab in a circular motion.
- Let your skin dry before injecting. Do not touch the injection site again before giving the injection.
- Do not fan or blow on the clean area.

A. Remove the needle cover

- Do not touch the plunger while you remove the needle cover.
- Hold the housing of the ORENCIA prefilled syringe with one hand and pull the needle cover straight off with your other hand (see Figure 6). **Do not** touch the plunger while you remove the needle cover.
- **Do not remove the needle cover until you are ready to inject ORENCIA. Inject ORENCIA as soon as possible after removing the needle cover.**

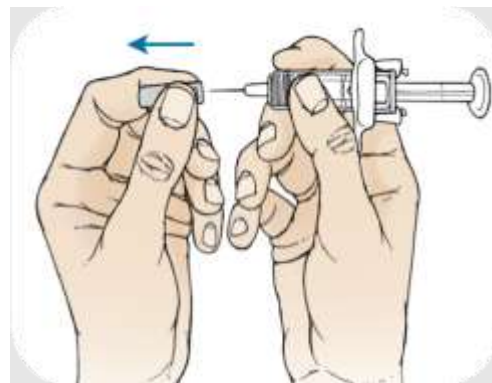


Figure 6

- Discard the needle cover in your household trash.
- There may be a small air bubble in the syringe tube containing the medication. There is no need to remove the air bubble.
- You may notice a drop of fluid leaving the needle. This is normal and will not affect your dose.
- Do not touch the needle or let it touch any surfaces.
- Do not use the prefilled syringe if it is dropped without the needle cover in place.

STEP 3: Inject ORENCIA

B. Position the prefilled syringe and inject ORENCIA

- Hold the housing of your prefilled syringe in one hand between the thumb and index finger (see Figure 7).



Figure 7

- Do not apply pressure to the plunger head until you are ready to begin your injection.
- Do not pull back on the plunger of the syringe at any time.
- Use your other hand and gently pinch the area of skin you cleansed. Hold firmly.
- Use a quick, dart-like motion to insert the needle into the pinched skin at a 45° angle (see Figure 8).

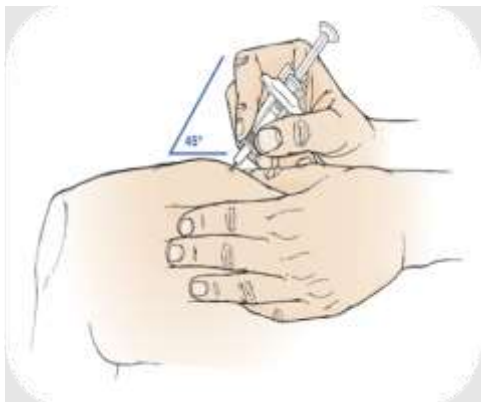


Figure 8

- To inject all of the medicine, use your thumb to push the plunger until the plunger head is

completely between the needle guard sides (see Figure 9).



Figure 9

- When the plunger is pushed in as far as it will go, continue to apply pressure to the plunger head (see Figure 9).
- Slowly remove your thumb from the plunger head. This allows the empty syringe to move up until the entire needle is covered by the needle guard (see Figure 10).
- Remove the needle from your skin and let go of the surrounding skin.



Figure 10

- Press a cotton ball over the injection site and hold for 10 seconds.
 - Do not rub the injection site. Slight bleeding is normal.
 - If needed, you may apply a small adhesive bandage to the injection site.

STEP 4: Disposal and record keeping

A. Dispose of your used syringe in a Sharps container.

- Sharps containers are special puncture-resistant disposal bins that can be purchased at many pharmacies.



Sharps container

- If you do not have a Sharps container, you may dispose of your used syringe in a puncture-resistant hard plastic or metal container that can be closed with a lid or cap, such as a laundry detergent bottle or coffee can. Do not use glass or clear plastic containers.
- Always keep your Sharps container out of reach of children and animals.
- Ask your doctor, nurse or pharmacist about provincial and local laws regarding the proper disposal of medical products that contain needles.
- Do not throw away your used prefilled syringes in your household trash or recycling bins.

B. Record your injection

- Write down the date, time and specific part of the body where you injected yourself. It may be helpful to write down any questions or concerns about the injection so you can ask your healthcare provider.

If you have questions or concerns about your ORENCIA prefilled syringe with BD UltraSafe Passive™ Needle Guard with Flange Extenders, please contact a healthcare provider familiar with ORENCIA.

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting the sponsor, Bristol-Myers Squibb Canada at 1-866-463-6267.

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