PRODUCT MONOGRAPH

Pr ORENCIA®

(abatacept)

Intravenous Infusion, 250 mg / 15 mL vial

Solution for Subcutaneous Injection, 125 mg / mL

Selective Co-stimulation Modulator

Bristol-Myers Squibb Canada
Montreal, Canada

Date of Preparation:
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Control No.: 203775

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ORENCIA®

(abatacept)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous Infusion (IV)	Vials 250 mg / 15 mL	See section DOSAGE FORMS, COMPOSITION AND PACKAGING
Subcutaneous Injection (SC)	Prefilled Syringes with BD UltraSafe Passive™ Needle Guard with Flange Extenders 125 mg/mL	
	Single-dose disposable ClickJect™ Prefilled Autoinjectors 125 mg/mL	

DESCRIPTION

ORENCIA (abatacept), a selective co-stimulation modulator, selectively modulates a key co-stimulatory signal required for full activation of T lymphocytes expressing CD28 (see ACTION AND CLINICAL PHARMACOLOGY). It is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to the modified Fc (hinge, CH2, and CH3 domains) portion of human immunoglobulin G1. ORENCIA is produced by recombinant DNA technology in a mammalian cell expression system.

INDICATIONS AND CLINICAL USE

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 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 ACTION and 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.

ORENCIA administered by SC injection has not been studied in children.

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 WARNINGS AND PRECAUTIONS, Infections).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Hypersensitivity

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

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.

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 ADVERSE REACTIONS: Infusion-related 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 ADVERSE REACTIONS: Infections).

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 ADVERSE REACTIONS: Infections).

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

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 DRUG INTERACTIONS – Drug-Laboratory Test Interaction).

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

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.

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 ADVERSE REACTIONS: Adverse Reactions in Adult Patients with COPD).

Information for Patients

Patients should be provided with Part III - Consumer 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.

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 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.

Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to ORENCIA, a pregnancy registry has been established. Healthcare professionals are encouraged to register patients by calling 1-877-311-8972.

Nursing Mothers

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.

Pediatric Use

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

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

ORENCIA administered by SC injection has not been studied in children.

Geriatric Use

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.

Hepatic Insufficiency

ORENCIA has not been studied in these patient populations. No dose recommendations can be made (see ACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics).

Renal Impairment

ORENCIA has not been studied in these patient populations. No dose recommendations can be made (see ACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics).

Malignancies

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 ADVERSE REACTIONS: Malignancies).

ADVERSE REACTIONS

1. CLINICAL EXPERIENCE IN ADULT RA PATIENTS TREATED WITH INTRAVENOUS AND SUBCUTANEOUS ORENCIA

Adverse Drug Reaction Overview

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

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

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%).

Clinical Trial Adverse Drug Reactions in Adult RA

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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

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

Related Adverse Event (Preferred Term)	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		

Table 1: Adverse Drug Reactions (ADRs) Occurring in ≥ 1% of Patients Treated with ORENCIA During Placebo-Controlled Double-Blind Rheumatoid Arthritis Studies*		
Related Adverse Event (Preferred Term)	**ORENCIA[c] n = 2653[a] %**	**Placebo[c] n = 1485[b] %**
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)

Less common Clinical Trial Adverse Drug Reactions (<1.0%)

ADRs reported in less than 1% of patients receiving ORENCIA in the double-blind clinical trials (n=2653) and not listed in **Table 1** 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, gastrooesophageal 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, gastrooesophagitis, 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, thyphoid 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, onychoclasis, 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.

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 (≥ 0.2%) with ORENCIA versus placebo were pneumonia (0.4% vs. 0.5%), (see WARNINGS AND PRECAUTIONS: Infections).

Other infections reported with a higher frequency (>0.5%) with ORENCIA compared to placebo, were rhinitis (2.4% vs. 1.3%), herpes zoester (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 WARNINGS AND PRECAUTIONS: Infections).

In post-marketing experience, opportunistic infections (including herpes zoster and *Pneumocystis jiroveci* 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 1.3 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 WARNINGS AND PRECAUTIONS: Malignancies).

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 events (>1.0%) with ORENCIA vs. placebo were 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, bronchopasm, , 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 WARNINGS AND PRECAUTIONS: Hypersensitivity)

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.

Immunogenicity

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.

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%]).

Clinical Trial Adverse Drug Reactions in MTX-Naive Patients

The AGREE (IM101023) study was an active-controlled clinical trial in MTX-naive patients. Subjects were randomized to receive abatacept or placebo for the first 12 months of treatment. In addition both groups received MTX (see 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 Orencia plus MTX group and 4 (1.6%) subjects in the Placebo plus MTX group.

Table 2 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 2: Adverse Drug Reactions (ADRs) Occurring in ≥ 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

Less common Clinical Trial Adverse Drug Reactions (<1.0%)

ADRs reported in less than 1% of patients receiving ORENCIA + MTX in the AGREE Trial and not listed in **Table 2** 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

2. CLINICAL EXPERIENCE IN 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 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 . 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.

Immunogenicity in 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.

Immunogenicity of 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 DOSAGE and ADMINISTRATION and ACTION and CLINICAL PHARMACOLOGY).

Immunogenicity of 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 DOSAGE and ADMINISTRATION and ACTION and CLINICAL PHARMACOLOGY).

Table 3: Adverse Drug Reactions (ADRs) Occurring in ≥ 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.

Less common Clinical Trial Adverse Drug Reactions (<1.0%)

ADRs reported in less than 1% of patients receiving SC ORENCIA in the IM101-174 Trial and not listed in **Table 3** 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, hemicephalalgia, 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, onychoclasis, 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

3. CLINICAL TRIAL ADVERSE DRUG REACTIONS IN JIA/JRA 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 WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS - Clinical Trial Adverse Drug Reactions in Adult RA).

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 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.

Table 4 below lists the adverse drug reactions (ADRs - adverse events at least possibly causally-related to treatment) occurring in ≥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 4: Adverse Drug Reactions (ADRs) Occurring in ≥ 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

Table 5 below lists the adverse drug reactions (ADRs - adverse events at least possibly causally-related to treatment) occurring in ≥1% of pediatric patients receiving ORENCIA in period B (double-blind phase) of the three part study conducted in children with polyarticular JIA.

Table 5: Adverse Drug Reactions (ADRs) Occurring in ≥ 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
Eosinophillia	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

Table 6 below lists the adverse drug reactions (ADRs - adverse events at least possibly causally-

related to treatment) occurring in ≥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 6: Adverse Drug Reactions (ADRs) Occurring in ≥ 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

Less Common Clinical Trial Adverse Reactions (<1%)

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 Tables 4 and 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

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.

Immunogenicity

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.

Malignancies

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

Postmarketing experience

Adverse reactions have been reported during the post-approval use of ORENCIA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to ORENCIA. 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.

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 ACTION AND CLINICAL PHARMACOLOGY: 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.

Drug-Laboratory Test Interaction

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 nicotine adenine dinucleotide (GDH-NAD), glucose oxidase, or glucose hexokinase test methods (see WARNINGS AND PRECAUTIONS – Blood Glucose Testing).

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

DOSAGE AND 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 7. 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 7: 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 7, 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 ACTION AND CLINICAL PHARMACOLOGY: 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.

Intravenous Infusion for Juvenile Idiopathic Arthritis/Juvenile Rheumatoid Arthritis

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.

Any unused portions in the vials must be immediately discarded.

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 2º -8º C before use.

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.

General Considerations for Subcutaneous Administration

ORENCIA Injection, 125 mg/syringe in both presentations (pre-filled syringe and autoinjector) are 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 or autoinjectors exhibiting particulate matter or discoloration. ORENCIA should be clear and colorless to pale yellow. Any leftover product remaining in the prefilled syringe or autoinjector should not be used.

Patients using ORENCIA for subcutaneous administration should be instructed to inject the full amount in the syringe or autoinjector (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.

OVERDOSAGE

For management of a suspected drug overdose, please contact your regional Poison Control Center.

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

ACTION AND CLINICAL PHARMACOLOGY

General

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 (TNFα), 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.

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 TNFα 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.

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 (Vss) ranged from 0.06 to 0.13 L/kg. The maximum serum concentration (Cmax) of abatacept following this dose was approximately 290 μg/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 Cmax 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 8: Pharmacokinetic parameters		
Parameter	**Value**	**Range**
Mean terminal half-life (t½)	13.1 days	8 - 25 days
Mean distribution volume (Vss)	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 μg/mL	22 - 29 μg/mL
Mean C_{max} concentrations	~290 μg/mL	171 - 398 μg/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) μg/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 Cmax 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 μg/mL for Cmax; 5875.5 vs. 41981.5μg*h/mL for AUC), but the mean Cmin at steady state was higher for SC vs. IV administration (32.5 vs. 22.3μg/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 μg/mL were

achieved after 6 to 8 weeks of weekly SC abatacept administration, and a mean trough concentration of 12.6 μg/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.

Patients in the sub-study (n=117) of the open-label extension of study IM101174 received 125 mg of SC abatacept administered weekly via the prefilled syringe for at least 4 months, and were then switched to receive 125 mg SC abatacept administered weekly via the prefilled autoinjector for 12 weeks. The adjusted geometric mean of abatacept at steady state trough concentration (Cminss) was 25.3 μg/mL for the SC prefilled autoinjector and 27.8 μg/mL for the SC prefilled syringe with a ratio of 0.91 [90% CI: 0.83, 1.00]. During the 12-week prefilled autoinjector treatment period, 1.7% (2/117) of patients using the SC prefilled autoinjector had local injection site reactions.

STORAGE AND STABILITY

ORENCIA (abatacept) lyophilized powder for IV Infusion 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 DOSAGE AND ADMINISTRATION).

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

SPECIAL HANDLING INSTRUCTIONS

Not applicable

DOSAGE FORMS, COMPOSITION AND PACKAGING

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. Each single-use vial of ORENCIA provides 250 mg abatacept, 500 mg maltose, 17.2 mg sodium phosphate monobasic, and 14.6 mg sodium chloride for administration.

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.

- **Single-dose disposable ClickJect™ Autoinjectors**

  Each single-dose disposable autoinjector 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, 27-gauge thin wall, ½-inch needle) covered with a rigid needle shield.8, 9

A sufficient excess of abatacept is incorporated into each pre-filled syringe or ClickJect™ Autoinjector to account for needle-syringe losses so that 1.0 mL of the solution containing 125 mg abatacept can be dispensed for subcutaneous injection. 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.

PART II: SCIENTIFIC INFORMATION

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 (C(1), 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 ≥ 5K 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.

pI: 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

$M^{-1}cm^{-1}$.

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 and in ClickJect™ Autoinjectors 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.

CLINICAL TRIALS

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 ≥ 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 9 summarizes the controlled clinical studies in patients with active rheumatoid arthritis.

Table 9: 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			
		Abatacept	90	48.3 (12.5)	74
		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			
		Abatacept	220	55.2 (12.0)	69
		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

Table 9: 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)
IM101174[a]	Randomized, double-blind, double-dummy, placebo-controlled study	MTX+placebo	253	49.7 (13.0)	79
		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-naive 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 naive 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 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 10.

Table 10: ACR Responses in Placebo-Controlled Trial with intravenous ORENCIA (Study IM103002)

	Percent of Patients	
	Inadequate Response to DMARDs	
Response Rate at Month 3	**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 11. 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 11: ACR Responses in Placebo-Controlled Trials with intravenous ORENCIA (Studies IM101100, AIM, ATTAIN)

	Percent of Patients					
	Inadequate Response to MTX				Inadequate Response to TNF Blocking Agents	
	IM101100		AIM		ATTAIN	
Response Rate	**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 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 12: ACR Response in Controlled Trial with subcutaneous ORENCIA (IM101-174)		
	Percent of Patients	
	Inadequate Response to MTX	
Response Rate	**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 Orencia, 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 13. In patients treated with ORENCIA, improvement was seen in all components through 6 and 12 months.

Table 13: 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]						

Table 13: 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
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 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 Questionaire; 0 = best, 3 = worst; 8 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.
[j] Health Assessment Questionaire; 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

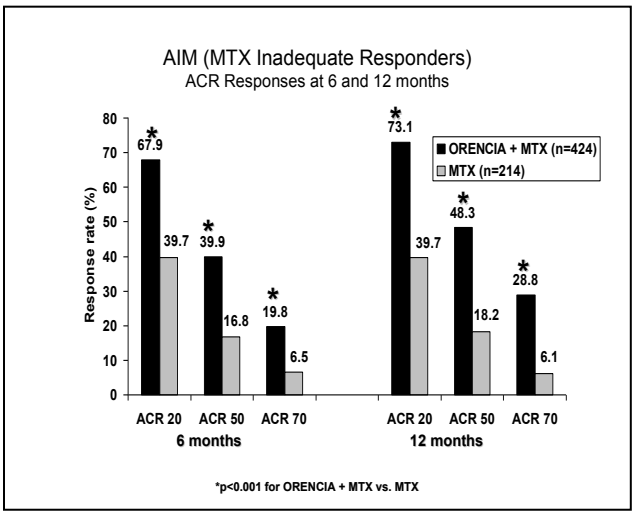
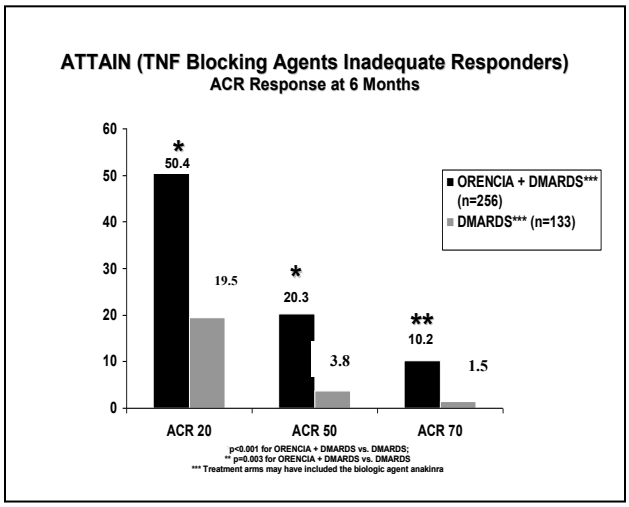


Figure 2



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

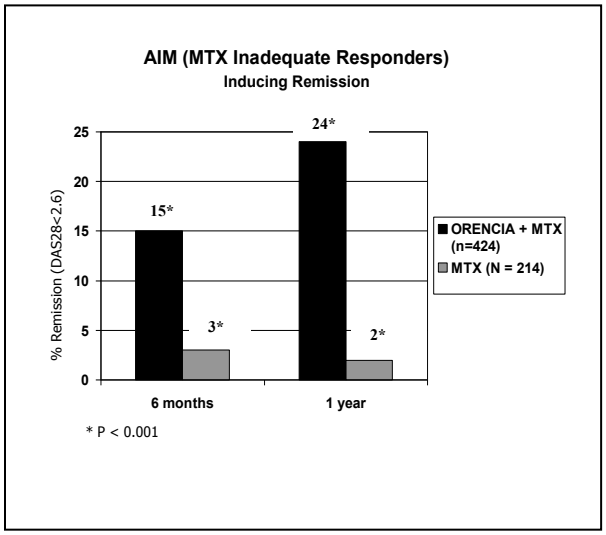
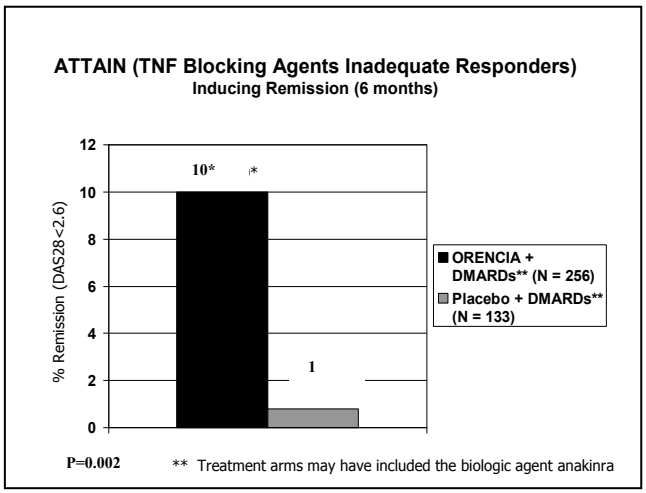


Figure 4



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 14. 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 14: 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 15: 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 16. 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 16: Mean Improvement from Baseline in Physical Function												
	Inadequate Response to Methotrexate								Inadequate Response to TNF Blocking Agents			
	IM101100				AIM				ATTAIN			
HAQ Disability Index	ORENCIA[a] + MTX		Placebo + MTX		ORENCIA[b] + MTX		Placebo + MTX		ORENCIA[b] + DMARDs[c]		Placebo + DMARDs[c]	
Mean baseline												
	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
Mean improvement from baseline												
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 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 Questionaire; 0 = best, 3 = worst; 8 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.
[e] Health Assessment Questionaire; 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.

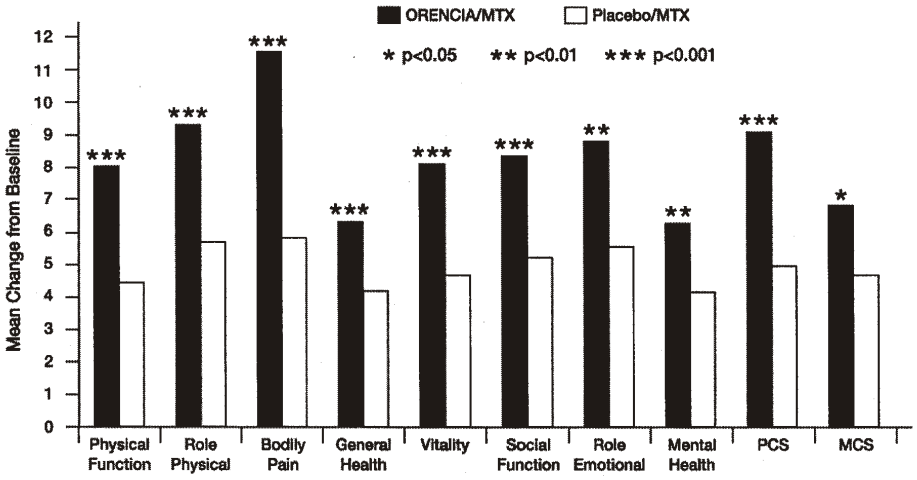
Health-Related Outcomes and Quality of Life

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



ORENCIA/MTX n = 424 Placebo/MTX n = 214

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.

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.

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.

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 sequellae, 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 Toxicity

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.

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PART III: CONSUMER INFORMATION

PrORENCIA®
or EN see ah
(abatacept)

This leaflet is Part III of a three-part "Product Monograph" published when ORENCIA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ORENCIA. Contact your doctor or pharmacist if you have any questions about this medication.

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.

ABOUT THIS MEDICATION

ORENCIA is a medicine used to treat rheumatoid arthritis (RA). It is supplied in vials for intravenous (IV) infusions (given through a needle placed in your arm vein), and in prefilled syringes or ClickJect™ prefilled autoinjectors 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 or autoinjector cannot be used for IV infusion.

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

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, the immune system attacks normal body tissues. This can cause damage and inflammation especially in the tissues of your joints. 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.

ORENCIA is used to treat:

- 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.

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

When it should not be used:

You should not take ORENCIA if you have:

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

What the medicinal ingredient is:

Abatacept.

- Each vial for IV infusion contains 250 mg abatacept.
- Each single-dose disposable prefilled syringe or autoinjector for subcutaneous (SC) administration contains 125 mg of abatacept per 1.0 mL of solution.

What the nonmedicinal ingredients are:

Intravenous formulation - inactive ingredients: Maltose, sodium chloride and sodium phosphate.

Subcutaneous formulation - inactive ingredients: Sucrose, poloxamer 188, monobasic sodium phosphate monohydrate, dibasic sodium phosphate anhydrous, water for injection.

What dosage forms it comes in:

Vials for IV use and single-dose disposable prefilled syringes or autoinjectors for SC administration.

How will ORENCIA be given to me and how often will I receive 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 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.
- 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.

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.

WARNINGS AND PRECAUTIONS

Information to know about serious side effects with ORENCIA

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.

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.

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 or autoinjector components do not contain any latex or dry natural rubber.

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®.

Before you receive treatment with ORENCIA you should tell your doctor 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.
- 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.

INTERACTIONS WITH THIS MEDICATION

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®.

PROPER USE OF THIS MEDICATION

Dose of ORENCIA

INTRAVENOUS INFUSION

Adults
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

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.

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 or autoinjector) regardless of how much you weigh. (See "Patient/Caregiver Instructions" for details.)

Overdose

In case of drug overdosage, contact a healthcare practitioner (e.g. doctor), hospital emergency department or regional poison control centre, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM		
Frequency	**Side Effect**	
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)	Talk with your healthcare provider if you have any symptoms of an infection.

This is not a complete list of side effects. If you have any

unexpected effects while taking ORENCIA, contact your doctor or pharmacist.

HOW TO STORE IT

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

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reactions reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

Note: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice

MORE INFORMATION

Pregnancy Registry: To monitor for outcomes of pregnant women exposed to ORENCIA, information is being collected about this. Speak to your healthcare professional for more information.

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.

This leaflet was prepared by Bristol-Myers Squibb Canada

Last revised: March 01, 2017

PATIENT/CAREGIVER INSTRUCTIONS FOR USE - ORENCIA (ABATACEPT) 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

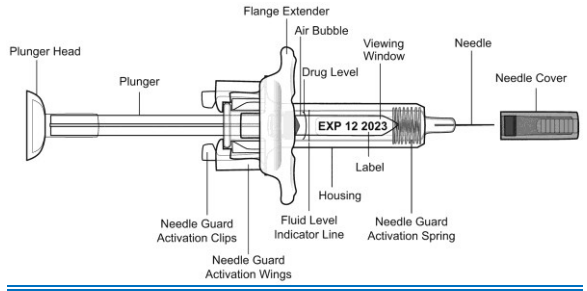


Figure 1

- 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).

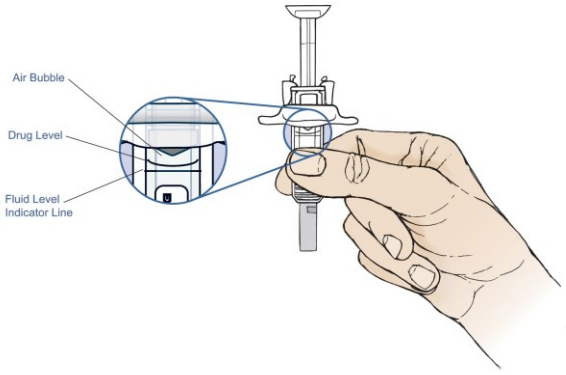


Figure 3

- 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 you skin is tender, bruised, red, scaly, or hard. Avoid any areas with scars or stretch marks.

Areas appropriate for self-injection and caregiver injection

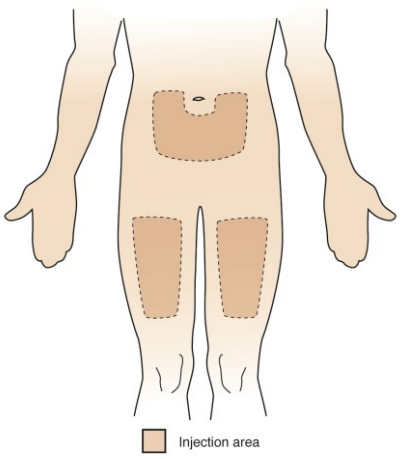


Figure 4

Additional injection area option for caregivers only

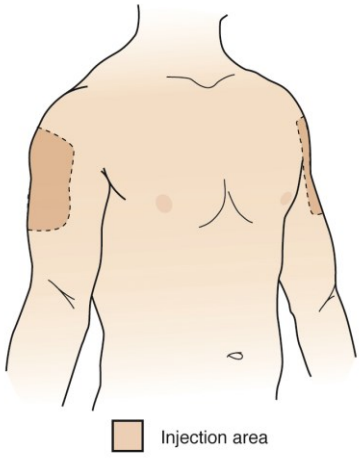


Figure 5

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.

STEP 3: Inject ORENCIA

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.**

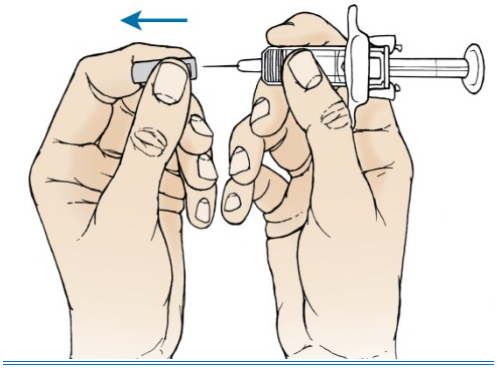


Figure 6

- 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.

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).

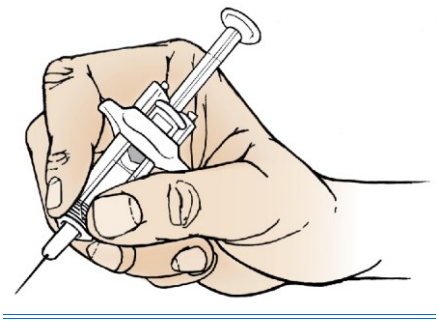


Figure 7

- 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).

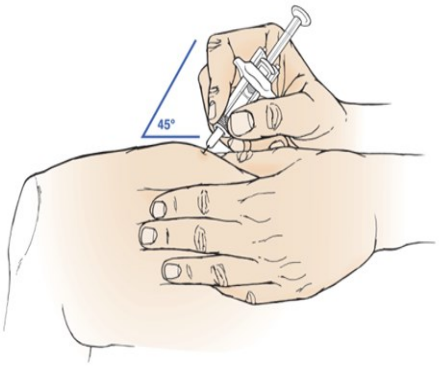


Figure 8

- 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).

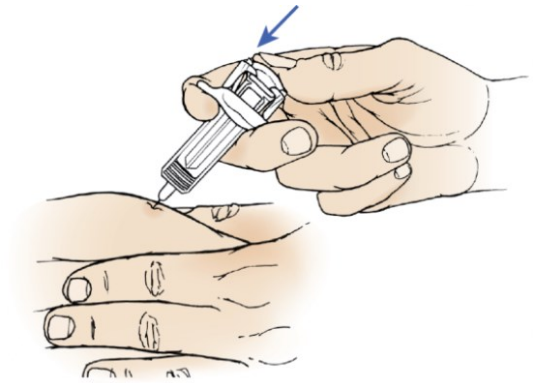


Figure 9

- 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.

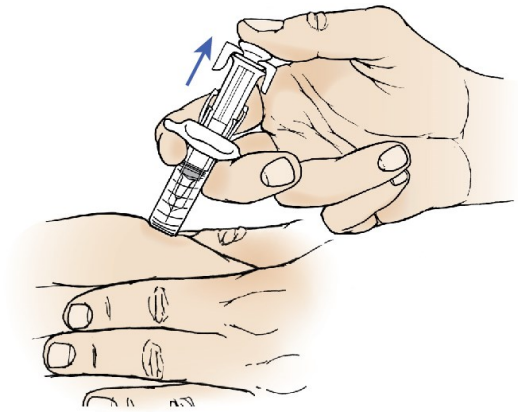


Figure 10

- 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.

This leaflet was prepared by Bristol-Myers Squibb Canada

Last Revised: March 01, 2017

PATIENT/CAREGIVER INSTRUCTIONS FOR USE
PRORENCIA® (ABATACEPT)
CLICKJECT™ PREFILLED AUTOINJECTOR

Getting started with ORENCIA therapy

Read these instructions before you use the ClickJect™ Prefilled Autoinjector and each time you get a refill. There may be new information. Before you use the Autoinjector for the first time, make sure your healthcare provider shows you the right way to use it.

Keep refrigerated until ready to use. **DO NOT FREEZE.**

Before You Begin

Get to know the CLICKJECT™ Autoinjector

- The autoinjector automatically delivers the medecine. The transparent tip locks over the needle once the injection is complete and the autoinjector is removed from the skin.
- **DO NOT remove the orange needle cover until you are ready to inject.**
- Keep away from children and pets.

Before Use

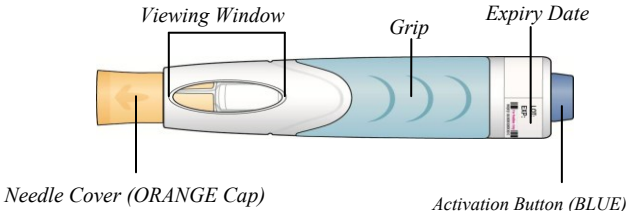


Figure 1

After Use

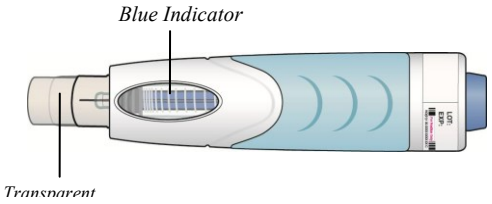


Figure 2

Before you use the Autoinjector

Do

- Remove the Autoinjector from the refrigerator 30 to 60 minutes prior to injecting.
- Have your additional injection supplies ready prior to injection: alcohol swabs, cotton ball or gauze, adhesive bandage and sharps container.

Don't

- Do not use the Autoinjector if cracked or broken.

STEP 1: Prepare Your Autoinjector

A. Let your Autoinjector warm up.

- Remove one Autoinjector from the refrigerator and let it rest at room temperature for **30 to 60 minutes.** Keep remaining unused Autoinjectors in their original carton in the refrigerator.

- **DO NOT** attempt to speed up the warming process by using a microwave or placing the autoinjector in warm water

- **DO NOT** remove the Autoinjector needle cover while allowing it to reach room temperature

- Find a comfortable space with a clean, flat working surface to gather your supplies

B. **Wash your hands well with soap & water.**

C. Examine the Autoinjector:

- **Check the expiration date** printed on the label. **DO NOT** use if past the expiration date.

- **Check the Autoinjector for damage**. **DO NOT** use if it is cracked or broken.

- **Check the liquid** through the viewing window. It should be clear to pale yellow. You may see a small air bubble. You do not need to remove it. **DO NOT inject** if the liquid is cloudy, discolored or has large particles.

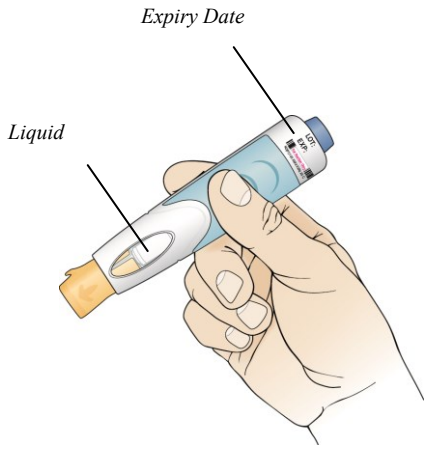


Figure 3

STEP 2: Prepare For injection

A. Choose your injection site in either the **abdomen,** front of the **thigh,** or outer area of upper arm (ONLY if given by a caregiver).

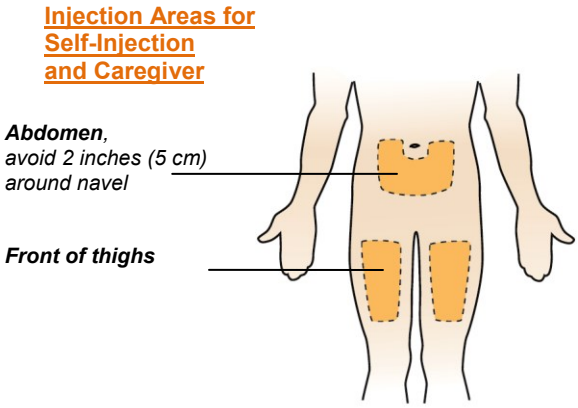


Figure 4

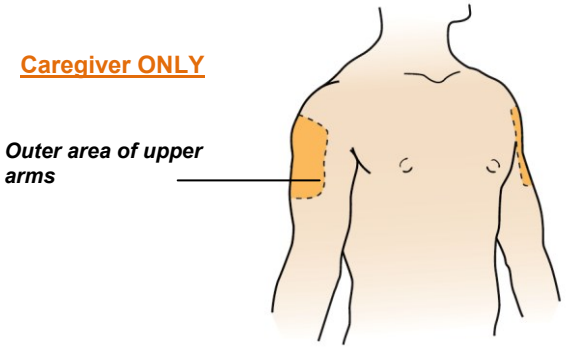


Figure 5

- Choose a different injection site for each new injection. You may use the same area of your body 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 an area where the skin is tender, bruised, red, scaly, or hard. Avoid any areas with scars or stretch marks.

B. Gently clean injection site with an alcohol swab in a circular motion. Let your skin dry. **Do not** touch, fan or blow the injection site.

C. **Pull orange needle cover STRAIGHT off.**

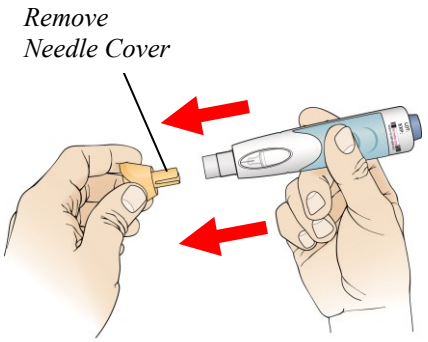


Figure 6

- **DO NOT** replace the cap on the autoinjector.
- Discard the cap in your household trash
- Inject ORENCIA as soon as possible after removing the needle cover.
- **DO NOT** use the Autoinjector if it is dropped after the cap is removed.
- It's normal to see a drop of fluid leaving the needle, it will not affect your dose.

STEP 3: INJECT YOUR DOSE

A. **Position the Autoinjector** so you can see the **viewing window** and it's at a 90° angle to the injection site. With your other hand, gently **pinch the cleaned skin**. (see Figure 7).

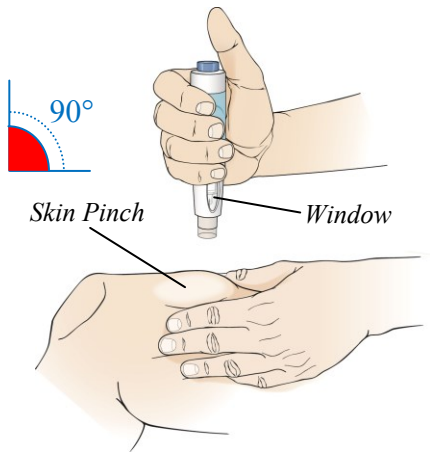


Figure 7

B. **Complete ALL steps for full-dose delivery:**

- **Push DOWN** on skin to unlock the autoinjector (see figure 8)

Figure 8

- **Press button**, **HOLD for 15 seconds AND watch the window** (see figure 9).

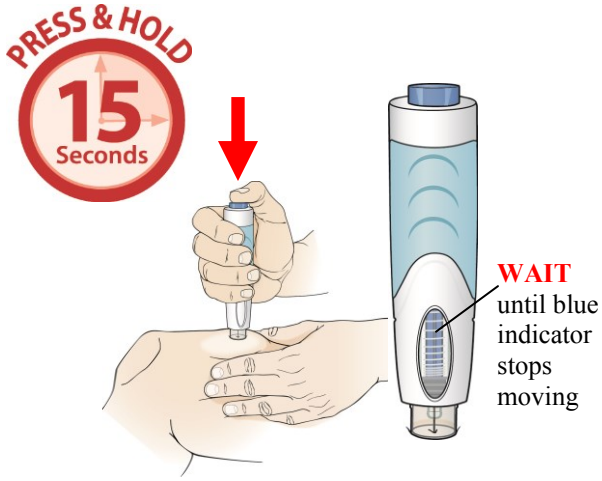


Figure 9

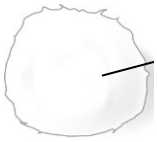
- You will hear a click as the injection begins
- For full-dose delivery, hold the Autoinjector in place for 15 seconds AND wait until the blue indicator stops moving in window.
- **Remove the Autoinjector** from the injection site by lifting it straight up. Once you remove

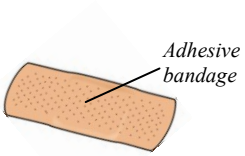
it from your skin, the transparent tip will lock over the needle. Release pinched skin

STEP 4: AFTER THE INJECTION

A. **Care of injection site:**

- Press a cotton ball over the injection site and hold for 10 seconds
- Slight bleeding is normal.
- **DO NOT** rub the injection site.
- If needed, you may cover the injection site with a small adhesive bandage.





B. Dispose of used Autoinjector into a Sharps container.

- Sharps containers are special puncture-resistant disposal bins that can be purchased at many pharmacies.
- Dispose of used ClickJect™ Autoinjector immediately after use.
- **DO NOT** throw into household trash or recycling bins
- **DO NOT** replace the cap on the used autoinjector.
- If your injection is administered by a caregiver, this person must also handle the autoinjector carefully to prevent accidental needle stick injury and possibly spreading infection.

Sharps container

- If you do not have a Sharps container, you may dispose of your used autoinjector 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.

C. **Record your injection**

- Write down the date, time, and site 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 ClickJect™ Autoinjector, 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.

This leaflet was prepared by Bristol-Myers Squibb Canada

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