DATA SHEET

1 PRODUCT NAME

ORENCIA® 250 mg powder for injection

ORENCIA 125 mg solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Abatacept is a fusion protein produced by recombinant DNA technology in Chinese hamster ovary cells.

ORENCIA 250 mg powder for injection.

Each vial contains 250 mg abatacept.

Excipient with known effect

Each vial contains 8.625 mg sodium.

ORENCIA 125mg solution for injection.

Each 1 mL pre-filled syringe or autoinjector contains 125 mg abatacept

Excipient with known effect

Each syringe or autoinjector contains 0.322 mg sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Lyophilized powder for IV infusion

ORENCIA is a sterile, white, preservative-free, lyophilized powder for parenteral administration. Following reconstitution with 10 mL of sterile water for injection, the solution of ORENCIA is clear, colourless to pale yellow, with a pH range of 7.2 to 7.8.

Solution for subcutaneous administration

ORENCIA, solution for injection, pre-filled syringe or autoinjector is supplied as a sterile, preservative-free, ready-to-use solution for subcutaneous injection. The subcutaneous solution is clear, colourless to pale yellow with a pH of 6.8 to 7.4.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ORENCIA in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have had an insufficient response or intolerance to other disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate or tumour necrosis factor (TNF) blocking agents. A reduction in the progression of joint damage and improvement in physical function have been demonstrated during combination treatment with ORENCIA and methotrexate.

ORENCIA in combination with methotrexate is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

ORENCIA is indicated for reducing signs and symptoms in paediatric patients 6 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). ORENCIA may be used

concomitantly with methotrexate (MTX). (There is no clinical trial data for the use of ORENCIA subcutaneous formulation in children, therefore its use in children cannot be recommended.)

ORENCIA is indicated for the treatment of active psoriatic arthritis (PsA) in adults when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. ORENCIA can be used with or without non-biologic DMARDs.

ORENCIA should not be administered concurrently with other biological DMARDs (eg, TNF inhibitors, rituximab, or anakinra).

4.2 Dose and method of administration

For adult patients with rheumatoid arthritis (RA) or psoriatic arthritis (PsA), ORENCIA may be administered as an intravenous (IV) infusion or a subcutaneous (SC) injection. MTX, other non-biologic DMARDs, corticosteroids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics may be used during treatment with ORENCIA.

IV dosing regimen

Rheumatoid Arthritis and Psoriatic Arthritis

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

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

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 administration.

For paediatric juvenile idiopathic arthritis, a dose calculated based on each patient's body weight is used (see below).

SC dosing regimen

Rheumatoid Arthritis

ORENCIA SC should be administered weekly at a dose of 125 mg by SC injection regardless of weight and may be initiated with or without an IV loading dose. For patients initiating therapy with an IV loading dose, ORENCIA should be initiated with a single IV infusion (based on body weight categories, see Table 1), followed by the first 125 mg SC injection administered within a day of the IV infusion

Patients switching from ORENCIA IV therapy to SC administration should administer the first SC dose instead of the next scheduled monthly IV dose.

Psoriatic Arthritis

ORENCIA SC should be administered weekly at a dose of 125 mg by SC injection without the need for an IV loading dose. ORENCIA can be used with or without non-biologic DMARDs.

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

Special populations

Renal impairment, hepatic impairment

ORENCIA has not been studied in these patient populations. No dose recommendations can be made.

Paediatric and adolescent

Juvenile Idiopathic Arthritis

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. Paediatric 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 IV 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.

There is no clinical trial data for the use of ORENCIA SC formulation in children, therefore its use in children cannot be recommended.

Use in the elderly

No dose adjustment is required (see section 4.4).

Concomitant therapy

MTX, other non-biologic DMARDs, corticosteroids, salicylates, NSAIDs, or analgesics may be used during treatment with ORENCIA.

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, BP. Immediately after reconstitution, the product must be further diluted to 100 mL with 0.9% sodium chloride injection, BP. To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary hold at 2 to 8 ºC for not more than 24 hours.

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 BP using the **SILICONE-FREE DISPOSABLE SYRINGE PROVIDED WITH EACH VIAL** and an 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 centre of the rubber stopper and direct the stream of sterile water for injection BP, to the glass wall of the vial. Do not use the vial if the vacuum is not present. To minimise foam formation in solutions of ORENCIA, the vial should be rotated with gentle swirling until the contents are completely dissolved. Avoid prolonged or vigorous agitation. 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 and colourless to pale yellow. Do not use if opaque particles, discolouration, or other foreign particles are present. After reconstitution, the concentration of abatacept in the vial will be 25 mg/mL.
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 BP, equal to the volume of the reconstituted ORENCIA. Slowly add the reconstituted ORENCIA solution from each vial to the infusion bag or bottle **USING ONLY the SILICONE-FREE DISPOSABLE SYRINGE PROVIDED WITH EACH VIAL**. Gently mix. **DO NOT SHAKE THE BAG OR BOTTLE**. The final concentration of abatacept in the bag or bottle

will depend upon the amount of drug added, but will be no more than 10 mg/mL. Any unused portion in the vials must be immediately discarded.

4. Prior to administration, the ORENCIA solution should be inspected visually for particulate matter and discolouration. Discard the solution if any particulate matter or discolouration is observed.
5. The entire, fully diluted ORENCIA solution should be administered over a period of 30 minutes and must be administered with an infusion set and a sterile, non-pyrogenic, low-protein-binding filter (pore size of 0.2 to 1.2 μm).
6. ORENCIA should not be infused concomitantly in the same IV line with other agents. No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of ORENCIA with other agents.
7. EACH VIAL OF ORENCIA IS FOR SINGLE USE IN ONE PATIENT ONLY. DISCARD ANY RESIDUE.

Preparation and Administration Instructions for Subcutaneous Injection

ORENCIA Solution for Injection, 125 mg/syringe or 125 mg/autoinjector, is not intended for IV infusion.

ORENCIA Solution for Injection is intended for use under the guidance of a physician or healthcare practitioner. The first dose should be done under medical supervision. Patients can self-inject after the treating physician/healthcare practitioner is assured that the patient's and/or carer's injection technique is satisfactory, and while providing medical follow-up as necessary.

After training in subcutaneous injection technique, the patient may self-inject ORENCIA**.** Patients should be instructed to follow the directions provided in the Patient/Caregiver Instructions for Use booklet for additional details on medication administration

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. Do not use ORENCIA prefilled syringes or autoinjectors exhibiting particulate matter or discolouration. ORENCIA should be clear and colourless to pale yellow. EACH PRE-FILLED SYRINGE OR AUTOINJECTOR OF ORENCIA IS FOR SINGLE USE IN ONE PATIENT ONLY. DISCARD ANY RESIDUE.

Patients using ORENCIA for SC 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/Caregiver Instructions for Use booklet.

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

For information on ORENCIA, contact Bristol-Myers Squibb 0800 167 567.

4.3 Contraindications

ORENCIA should not be administered to patients with known hypersensitivity to ORENCIA or any of its components (see section 2 and 6.1). ORENCIA should not be administered to patients with severe infections such as sepsis, abscesses, tuberculosis, and opportunistic infections.

4.4 Special warnings and precautions for use

Combination with TNF blocking agents

There is limited experience with the use of ORENCIA in combination with TNF blocking agents. In placebo-controlled clinical trials in patients with adult RA, patients receiving concomitant IV ORENCIA and TNF blocking agent therapy experienced more infections (24%) and serious infections (2.2%) compared to patients treated with only TNF blocking agents (19% and 0.8%, respectively). Concurrent therapy with ORENCIA and a TNF blocking agent is not recommended.

While transitioning from TNF blocking agent therapy to ORENCIA therapy, patients should be monitored for signs of infection.

Other biologic RA therapy

There is insufficient experience to assess the safety and efficacy of ORENCIA administered concurrently with other biologic RA therapy, such as anakinra or rituximab, and therefore, such use is not recommended.

Hypersensitivity

Hypersensitivity reactions can be observed during treatment with any injectable protein. Such reactions have been reported with ORENCIA IV administration in clinical trials, where patients were not required to be pretreated to prevent hypersensitivity reactions. The occurrence of anaphylaxis remained rare throughout the double blind trials and cumulative periods. Hypersensitivity was reported uncommonly. Other events potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnoea, that occurred within 24 hours of ORENCIA infusion, were uncommon (see section 4.8). Anaphylaxis or anaphylactoid reactions can occur after the first infusion and can be life-threatening. In postmarketing 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.

Effects on the immune system

The possibility exists for drugs that affect the immune system, including ORENCIA, to affect vaccination responses and host defenses against infections and malignancies.

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. Physicians should exercise caution when considering the use of ORENCIA in patients with: a history of recurrent infections; underlying conditions which may predispose them to infections; or chronic, latent, or localised 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. A higher rate of serious infections has been observed in adult RA patients treated with concurrent TNF blocking agents and ORENCIA.

In placebo-controlled clinical studies in adults with RA, of 2653 ORENCIA patients and 1485 placebo patients, two cases of tuberculosis were reported, one each in the ORENCIA and placebo groups. When treating patients with therapies that modulate the immune system, it is appropriate to screen for tuberculosis infections, as was the case with patients in these clinical trials. ORENCIA has not been studied in patients with a positive tuberculosis screen, and the safety of ORENCIA in individuals with latent tuberculosis is unknown. Patients testing positive in tuberculosis screening, should be treated by 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.

Malignancies

In the placebo-controlled clinical trials in adult RA, the frequencies of malignancies in abatacept- and placebo-treated patients were 1.2% and 0.9%, respectively (see section 4.8). Patients with known

malignancies were not included in these clinical trials. In carcinogenicity studies in mice, an increase in lymphomas and mammary tumours were noted. The clinical significance of this observation is unknown (see section 5.3). The potential role of ORENCIA in the development of malignancies, including lymphoma, in humans is unknown. There have been reports of non-melanoma skin cancers in patients receiving ORENCIA (see section 4.8). Periodic skin examination is recommended for all patients, particularly for those with risk factors for skin cancer.

Immunisations

Live vaccines should not be given concurrently with ORENCIA or within 3 months of its discontinuation. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving ORENCIA. Drugs that affect the immune system, including ORENCIA, may blunt the effectiveness of some immunisations. 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, a majority of ORENCIA-treated patients (62/112) 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 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 titres to trivalent influenza vaccine.

In a small study with healthy subjects, ORENCIA reduced the quantitative immune response (measured via antibody titre against the tetanus toxoid vaccine antigen). However the 2-fold increase in titre response to this antigen was not altered.

It is recommended that patients with juvenile idiopathic arthritis be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating ORENCIA therapy.

Autoimmune processes

There is a theoretical concern that treatment with ORENCIA might increase the risk for autoimmune processes, for example, deterioration of multiple sclerosis. In the placebo-controlled clinical trials, abatacept treatment did not lead to increased autoantibody formation, such as antinuclear and anti-dsDNA antibodies, relative to placebo treatment.

Paediatric use

ORENCIA is indicated for reducing signs and symptoms in paediatric patients 6 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis who have had an inadequate response to one or more DMARDs. ORENCIA may be used concomitantly with MTX.

The safety and effectiveness of ORENCIA in paediatric patients below 6 years of age have not been established. Therefore, ORENCIA is not recommended for use in patients below the age of 6 years.

Safety and efficacy of ORENCIA in paediatric patients for uses other than juvenile idiopathic arthritis have not been established.

There is no clinical trial data for the use of ORENCIA SC formulation in children, therefore its use in children cannot be recommended.

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

Non-clinical studies relevant for use in the paediatric population

Studies in rats exposed to abatacept have shown immune system abnormalities including a low incidence of infections leading to death (juvenile rats) as well as inflammation of the thyroid and pancreas (both juvenile and adult rats). Studies in adult mice and monkeys have not demonstrated similar findings. The increased susceptibility to opportunistic infections observed in juvenile rats is likely associated with the exposure to abatacept prior to development of memory responses. The relevance of these results to humans greater than 6 years of age, where memory responses have more time to develop, is unknown.

Use in the elderly

A total of 404 patients 65 years of age and older, including 67 patients 75 years and older, received ORENCIA in placebo-controlled clinical studies. 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. Because there is a higher incidence of infections and malignancies in the elderly population in general, caution should be used when treating the elderly.

Patients on controlled sodium diet

This medicinal product contains 1.5 mmol (or 34.5 mg) sodium per maximum dose of 4 vials (0.375 mmol or 8.625 mg sodium per vial). To be taken into consideration when treating patients on a controlled sodium diet.

Use in patients with psoriatic skin lesions

Use of ORENCIA in PsA should be limited to patients for whom additional systemic therapy for psoriatic skin lesions is not required.

Use in patients with chronic obstructive pulmonary disease (COPD)

COPD adult patients treated with ORENCIA developed adverse events more frequently than those treated with placebo, including COPD exacerbations, cough, rhonchi, and dyspnoea. 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.

Subcutaneous injections

The first dose should be done under medical supervision. Patients can self-inject after the treating physician/healthcare practitioner is assured that the patient's and/or carer's injection technique is satisfactory, and while providing medical follow-up as necessary (see section 4.2).

Information for patients

Patients should be provided the ORENCIA Consumer Medicine Information (CMI) and be provided an opportunity to read it prior to each treatment session. Because caution should be exercised in administering ORENCIA to patients with active infections, it is important that the patient's overall health be assessed at each visit and any questions resulting from the patient's reading of the CMI be discussed.

Effects on laboratory tests

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 IV administration, resulting in falsely elevated blood glucose readings on the day of infusion. When receiving ORENCIA for intravenous administration, patients that require blood glucose monitoring should be advised to consider methods that do not react with maltose, such as those based on glucose dehydrogenase nicotine adenine dinucleotide (GDH-NAD), glucose oxidase, or glucose hexokinase test methods.

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

4.5 Interaction with other medicines and other forms of interaction

Formal drug interaction studies have not been conducted with ORENCIA.

The majority of patients in the RA placebo-controlled clinical trials received concomitant DMARDs, NSAIDs, and/or corticosteroids. Most patients were taking MTX. Other less frequently used concomitant DMARDs included chloroquine/hydroxychloroquine, sulfasalazine, and leflunomide. There is limited experience with abatacept in combination with other DMARDs such as azathioprine, gold and anakinra. Population pharmacokinetic analyses revealed that MTX, NSAIDs, corticosteroids, and TNF blocking agents did not influence abatacept clearance (see section 5.2).

Concurrent administration of a TNF blocking agent with ORENCIA has been associated with an increased risk of serious infections. Concurrent therapy with ORENCIA and TNF blocking agents is not recommended.

There is insufficient experience to assess the safety and efficacy of ORENCIA administered concurrently with anakinra or rituximab, and therefore such use is not recommended.

ORENCIA has not been studied in combination with agents which deplete lymphocyte count. Such combination therapy could potentiate the effects of ORENCIA on the immune system.

4.6 Fertility, pregnancy and lactation

Pregnancy (Category C)

There are no adequate and well-controlled studies in pregnant women. The use of ORENCIA during pregnancy is not recommended. Abatacept may affect the immune system in the foetus (see section 5.3).

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.

Breast-feeding

Abatacept has been shown to be present in rat milk and in the serum of suckling pups. 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 breast-fed infants from abatacept, women on abatacept should not breast feed. The long half-life of abatacept should also be considered when discontinuing therapy.

Fertility

Fertility in rats was unaffected by abatacept doses of up to 200 mg/kg every 3 days (11-fold the human drug exposure based on AUC).

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Undesirable effects

Clinical trial experience in adult Rheumatoid Arthritis (RA) patients treated with intravenous and subcutaneous ORENCIA

ORENCIA has been studied in patients with active RA in nine placebo-controlled clinical trials (2653 patients with ORENCIA, 1485 with placebo). Most patients in these trials were taking MTX (67.8% with ORENCIA, 63.0% with placebo). Other concomitant medications included: NSAIDs (79.0% with ORENCIA, 79.6% with placebo); systemic corticosteroids (51.6% with ORENCIA, 49.4% with placebo); non-biological DMARD therapy, most commonly chloroquine/hydroxychloroquine (8.6% with ORENCIA, 9.8% with placebo), leflunomide (5.1% with ORENCIA, 5.0% with placebo) and sulfasalazine (5.8% with ORENCIA, 5.3% with placebo); TNF blocking agents, mainly etanercept (6.2% with ORENCIA, 5.0% with placebo); and anakinra (0.8% with ORENCIA, 0.7% with placebo).

In placebo-controlled clinical trials with ORENCIA, adverse drug reactions (ADRs) (adverse events at least possibly causally-related to treatment) were reported in 49.4% of ORENCIA-treated patients and 45.8% of placebo-treated patients. The most frequently reported adverse drug reactions (≥ 5%) among ORENCIA-treated patients were headache and nausea. The proportion of patients who discontinued treatment due to ADRs was 3.0% for ORENCIA-treated patients and 2.0% for placebo-treated patients.

Overall adverse events reported irrespective of consideration to causality to treatment in the placebo-controlled clinical trials in RA patients are listed in Table 2.

The majority of these adverse events were mild to moderate and the severity was similar in patients that had previously taken traditional DMARDs, such as MTX, or biological therapies, such as TNF blocking agents (Table 3).

Table 2 : Overview of Adverse Events in Placebo-Controlled Clinical Trials in RA Patients

	ORENCIA n=2653 %	Placebo n=1485 %
All adverse events	88.0	84.7
Serious adverse events	12.5	11.7
Infections and infestations	54.3	51.6
Malignancies	1.2	0.9
Acute infusion-related events (reported within 1 hour of the start of the infusion)*	6.4	4.7

*IV administration only, where n=2367 and 1352 for ORENCIA and Placebo, respectively.

Table 3: Intensity of Adverse Events in Double-Blind, Controlled Study Periods: Study IV vs Study III

	Percent of Patients			
	Mild	Moderate	Severe	Very Severe

Table 3: Intensity of Adverse Events in Double-Blind, Controlled Study Periods: Study IV vs Study III

	Percent of Patients			
Study IV, Inadequate Response to TNF Blocking Agent				
ORENCIA	61.2%	47.3%	8.1%	1.9%
Placebo	51.1%	42.1%	9.8 %	0.8%
Study III, Inadequate Response to MTX				
ORENCIA	75.1%	60.3%	15.2%	1.2%
Placebo	73.5%	55.3%	12.8%	0.9%

In general, adverse events are more common with biological agents as compared with other types of medications used in the management of RA.

Adverse drug reactions greater in frequency (difference >0.2%) in ORENCIA-treated patients compared to placebo patients in nine IV and SC placebo-controlled RA clinical trials are listed below by system organ class and frequency (very common ≥10%; common ≥1% - <10%; uncommon ≥0.1% - <1%).

Infections and infestations

Very Common:	Upper respiratory tract infection (including tracheitis, nasopharyngitis and sinusitis)
Common:	Lower respiratory tract infection (including, bronchitis), urinary tract infection, herpes infections (including herpes simplex, oral herpes and herpes zoster), pneumonia
Uncommon:	Tooth infection, infected skin ulcer, onychomycosis, rhinitis, ear infection, pyelonephritis

Neoplasms benign and malignant (including cysts and polyps)

Uncommon:	Basal cell carcinoma

Blood and the lymphatic system disorders

Uncommon:	Leukopenia, thrombocytopenia

Immune system disorders

Uncommon:	Hypersensitivity

Psychiatric disorders

Uncommon:	Depression, anxiety, sleep disorder (insomnia)

Nervous system disorders

Common:	Headache, dizziness
Uncommon:	Paraesthesia

Eye disorders

Uncommon:	Conjunctivitis, visual acuity reduced

Ear and labyrinth disorders

Uncommon:	Vertigo

Cardiac disorders

Uncommon:	Tachycardia, bradycardia, palpitations

Vascular disorders

Common:	Hypertension
Uncommon:	Hypotension, hot flush, flushing

Respiratory, thoracic and mediastinal disorders

Common:	Cough
Uncommon:	Chronic obstructive pulmonary disease exacerbation

Gastrointestinal disorders

Common:	Abdominal pain, diarrhoea, nausea, dyspepsia, mouth ulceration, aphthous stomatitis
Uncommon:	Gastritis

Skin and subcutaneous tissue disorders

Common:	Rash (including dermatitis)
Uncommon:	Increased tendency to bruise, dry skin, hyperhidrosis, erythema, acne, alopecia

Musculoskeletal, connective tissue and bone disorders

Uncommon:	Arthralgia, pain in extremity

Reproductive system and breast disorders

Uncommon:	Amenorrhea, menorrhagia

General disorders and administration site conditions

Common:	Fatigue, asthenia, local injection site reaction[a]
Uncommon:	Influenza-like illness

Investigations

Common:	Blood pressure increased, liver function test abnormal (including transaminases increased)
Uncommon:	Blood pressure decreased, weight increased

[a] SC administration only

Infections

In the placebo-controlled trials, infections at least possibly related to treatment were reported in 22.7% of ORENCIA-treated patients and 20.5% of placebo patients.

AEs reported in patients treated by abatacept IV or SC which did not occur with an excess incidence (i.e. the difference was not >0.2%) over placebo but were considered to be medically relevant based on

the overall clinical experience included sinusitis (common), pelvic inflammatory disease (uncommon) and urosepsis (uncommon).

Serious infections at least possibly related to treatment were reported in 1.5% of ORENCIA-treated patients and 1.1% of placebo patients. The incidence rates (95% CI) for serious infections were 3.0 (2.3, 3.8) per 100 patient-years for ORENCIA-treated patients and 2.3 (1.5, 3.3) per 100 patient-years for placebo-treated patients in the double-blind studies. The most frequent (0.1-0.4%) serious infections at least possibly related to treatment reported with ORENCIA were pneumonia, cellulitis, localised infection, urinary tract infection, bronchitis, diverticulitis, and acute pyelonephritis (see section 4.4).

In the cumulative period in clinical trials in 7,044 patients treated with abatacept during 20,510 patient-years, the incidence rate of serious infections was 2.4 per 100 patient-years, and the annualised incidence rate remained stable.

Malignancies

In the placebo-controlled clinical trials, malignancies were reported in 1.2% (31/2653) of ORENCIA-treated patients, and in 0.9% (14/1485) of placebo-treated patients (see section 4.4).

In the cumulative period in 7,044 patients treated with ORENCIA during 21,011 patient-years, (of which over 1,000 were treated with abatacept for over 5 years), the incidence rate of malignancy was 1.2 (1.1, 1.4) per 100 patient-years, and the annualised incidence rate remained stable.

The most frequently reported malignancy in the placebo-controlled clinical trials was non-melanoma skin cancer; 0.6 (0.3, 1.0) per 100 patient-years for abatacept-treated patients, 0.4 (0.1, 0.9) per 100 patient-years for placebo-treated patients, and 0.5 (0.4, 0.6) per 100 patient-years in the cumulative period.

The most frequently reported solid organ cancer in the placebo-controlled trials was lung cancer, 0.17 (0.05, 0.43) per 100 patient-years, for abatacept-treated patients, 0 for placebo-treated patients, and 0.12 (0.08, 0.17) per 100 patient-years in the cumulative period.

The most common haematologic malignancy was lymphoma, 0.04 (0, 0.24) per 100 patient-years for abatacept-treated patients, 0 for placebo-treated patients, and 0.06 (0.03, 0.1) per 100 patient-years in the cumulative period. .

Infusion-related reactions and hypersensitivity reactions

Infusion-related reactions can be observed during treatment with any injectable protein. Such reactions have been reported with ORENCIA administration in clinical trials, where patients were not required to be pre-treated to prevent hypersensitivity reactions.

For acute infusion reactions (within 1 hour of infusion), the incidence rate was 7.66 per 100 patient-years. The annual incidence rate of acute-infusional events was elevated in the first year of exposure, decreased in the second, and then remained stable with increasing duration of exposure to abatacept. The 4 most common events contributing to this incidence rate per 100 patient-years were dizziness (2.39), nausea (1.02), flushing (0.67), and hypotension (0.53). The frequencies of these 4 events were 2.1%, 0.9%, 0.6%, and 0.5%, respectively. Greater than 90% of all subjects with acute-infusional events were mild or moderate in intensity.

For peri-infusion reactions (up to 24 hours after infusion), the incidence rate was 19.19 per 100 patient-years. The 5 most common events contributing to this incidence rate per 100 patient-years were dizziness (5.18), nausea (5.03), flushing (1.02), vomiting (0.82) and rash (0.82).

Adverse drug reactions in patients with chronic obstructive pulmonary disease (COPD)

In Study V, there were 37 patients with COPD treated with ORENCIA and 17 treated with placebo. The COPD patients treated with ORENCIA developed adverse drug reactions more frequently than those treated with placebo (51.4% vs. 47.1%, respectively). Respiratory disorders occurred more frequently in ORENCIA-treated patients than in placebo-treated patients (10.8% vs. 5.9%, respectively); these included COPD exacerbation, and dyspnoea. A greater percentage of ORENCIA-

than placebo-treated patients with COPD developed a serious adverse reaction (5.4% vs. 0%), including COPD exacerbation (1 of 37 patients [2.7%]) and bronchitis (1 of 37 patients [2.7%]).

Autoimmune processes

ORENCIA therapy did not lead to increased formation of antinuclear or anti-double stranded DNA antibodies compared with placebo.

The incidence rate of autoimmune disorders in abatacept-treated patients during the double-blind period was 8.8 (7.6, 10.1) per 100 patient-years of exposure and for placebo-treated patients was 9.6 (7.9, 11.5) per 100 patient-years of exposure. The incidence rate in abatacept-treated patients was 3.8 per 100 patient-years in the cumulative period.

The most frequently reported autoimmune-related disorders other than the indication being studied during the cumulative period were psoriasis, rheumatoid nodule, and Sjogren's syndrome.

Immunogenicity

Antibodies directed against the ORENCIA molecule were assessed by ELISA assays in 3,985 rheumatoid arthritis patients treated for up to 8 years with ORENCIA. One hundred and eighty-seven of 3,877 patients developed anti-abatacept antibodies while on treatment. In patients assessed for anti-abatacept antibodies after discontinuation of ORENCIA (>42 days after last dose), 103 of-1,888 (5.5%) were seropositive.

Samples with confirmed binding activity to CTLA-4 were assessed for the presence of neutralising antibodies. Twenty-two of 48 evaluable patients showed significant neutralising activity. The potential clinical relevance of neutralising antibody formation is not known.

Overall, there was no apparent correlation of antibody development to clinical response or adverse events. However, the number of patients that developed antibodies was too limited to make a definitive assessment.

Clinical experience in MTX-naive patients

Study VI was an active-controlled clinical trial in MTX-naive patients. Data from Study VI were not integrated into the safety dataset described above in this section; however, the safety experience in MTX-naive patients was consistent with that described above in patients with an inadequate response to MTX or a TNF blocking agent. The adverse reaction profile observed in patients receiving MTX alone in Study VI was as expected, and the adverse reaction profile observed in patients receiving ORENCIA+MTX was similar to that in patients receiving MTX alone.

Study VII: Abatacept or infliximab versus placebo

At 6 months, the overall serious adverse events considered to be related to treatment was 1.9% (3 patients) in the abatacept group, 4.8% (8) in the infliximab group, and 2.7% (3) in the placebo group. The frequency of serious infections was 1.3% (2) in the abatacept group, 2.4% (4) in the infliximab group, and 0.9% (1) in the placebo group. The frequency of acute infusional adverse events was 5.1% (8) in the abatacept group, 18.2% (30) in the infliximab group, and 10.0% (11) in the placebo group. At 12 months, the overall serious adverse events considered to be related to treatment was 3.2% (5) in the abatacept group and 8.5% (14) in the infliximab group. The frequency of serious infections was 1.3% (2) in the abatacept group and 6.1% (10) in the infliximab group, with a total of 5 serious opportunistic infections in the infliximab group and none in the abatacept group. With regard to abnormal laboratory values at 6 months, antinuclear antibodies developed in 1.7% (2) of the abatacept group, 32.2% (38) of the infliximab group, and 4.9% (4) of the placebo group.

Clinical trial experience in adult RA patients treated with subcutaneous ORENCIA

In general, the adverse reactions in adult RA patients treated with SC abatacept were similar in type to those seen in patients treated with abatacept administered intravenously.

Study SC-I was a randomised, double-blind, double-dummy, non-inferiority study that compared the efficacy and safety of abatacept administered subcutaneously (with IV loading dose) and intravenously in 1457 subjects with RA, receiving background MTX, and experiencing an inadequate response to MTX (MTX-IR). The safety experience and immunogenicity for ORENCIA administered subcutaneously was consistent with intravenous Studies I-VI. Due to the route of administration, injection site reactions and immunogenicity were evaluated and are discussed in the sections below.

A subgroup analysis, although limited by assessments involving small numbers and the lack of a comparator, did not reveal any unexpected safety concerns. The finding that more AEs were reported subjects >100 kg both for IV and SC abatacept may reflect small numbers of subjects in some subgroups and differences in exposure.

Study SC-IV was a randomised, investigator-blinded, non-inferiority study that compared the efficacy and safety of SC abatacept (without IV loading dose) and adalimumab in subjects with moderate to severely active RA, receiving background MTX, and experiencing an inadequate response to MTX (MTX-IR) (see section 5.1). The safety experience for ORENCIA administered subcutaneously was consistent with subcutaneous Study SC-I.

Injection site reactions in adult RA patients treated with SC abatacept

Study SC-I compared the safety of abatacept including injection site reactions following SC or IV administration. The overall frequency of injection site reactions was 2.6% (19/736) and 2.5% (18/721) for the SC abatacept group and the IV abatacept group (SC placebo), respectively. All injection site reactions were described as mild to moderate (haematoma, pruritus, or erythema) and generally did not necessitate drug discontinuation.

Study SC-IV compared the safety of SC abatacept and adalimumab including injection site reactions following SC administration. The frequency of injection site reactions were 3.8% (12/318) and 9.1% (30/328) at 12 months (p=0.006) and 4.1% (13/318) and 10.4% (34/328) at 24 months for abatacept SC and adalimumab SC, respectively.

During the cumulative period including all subjects treated with abatacept in seven SC studies, the frequency of injection site reactions was 4.6% (116/2538) with an incidence rate of 1.32 per 100 person-years.

Immunogenicity in adult RA patients treated with SC abatacept

Study SC-I compared the immunogenicity to abatacept following SC or IV administration. The overall immunogenicity frequency to abatacept was 1.1% (8/725) and 2.3% (16/710) for the SC and IV groups, respectively. The rate is consistent with previous experience, and there was no effect of immunogenicity on pharmacokinetics, safety, or efficacy.

Immunogenicity and safety of SC abatacept administration as monotherapy without an IV loading dose

Study SC-II was conducted to determine the effect of monotherapy use of ORENCIA on immunogenicity following SC administration without an IV load in 100 RA patients, who had not previously received abatacept or other CTLA4Ig, who received either SC ORENCIA+MTX (n=51) or SC ORENCIA monotherapy (n=49). No patients in either group developed anti-abatacept antibodies after 4 months of treatment. The safety observed in this study was consistent with that observed in the other SC studies.

Immunogenicity and safety of SC abatacept upon withdrawal (three months) and restart of treatment

Study SC-III in the SC program was conducted to investigate the effect of withdrawal (three months) and restart of ORENCIA SC treatment on immunogenicity in RA patients treated concomitantly with MTX. One hundred sixty-seven patients were enrolled in the first 3-month treatment period and responders (n=120) were randomised to either SC ORENCIA or placebo for the second 3-month period (withdrawal period). Patients from this period then received open-label ORENCIA treatment in the final 3-month period of the study (Period 3). At the end of the withdrawal period, 0/38 patients who continued

to receive SC ORENCIA developed anti-abatacept antibodies compared to 7/73 (9.6%) of patients who had SC ORENCIA withdrawn during this period. Half of the patients receiving SC placebo during the withdrawal period received a single IV infusion of ORENCIA at the start of Period 3 and half received IV placebo prior to reinitiating SC ORENCIA in Period 3. At the end of Period 3, when all patients again received SC ORENCIA, the immunogenicity rates were 1/38 (2.6%) in the group receiving SC ORENCIA throughout, and 2/73 (2.7%) in the group that had received placebo during the withdrawal period. Upon reinitiating therapy, there were no injection reactions and no differences in response to therapy in patients who were withdrawn from SC therapy for up to 3 months relative to those who remained on SC therapy, whether therapy was reintroduced with or without an IV loading dose. The safety observed in this study was consistent with that observed in the other studies.

Study SC-IV: Additional safety information for SC abatacept versus adalimumab.

Safety and structural damage assessments were conducted at one and two years. The overall safety profile with respect to adverse events was similar between the two groups over the 24-month period. After 24 months, adverse reactions were reported in 41.5% (132/318) and 50% (164/328) of abatacept- and adalimumab-treated patients. Serious adverse reactions were reported in 3.5% (11/318) and 6.1% (20/328) of the respective group. At 24 months, 20.8% (66/318) in the SC abatacept group and 25.3% (83/328) in the adalimumab group had discontinued.

At 24 months, 1.6% (5/318) patients in the SC abatacept group and 4.9% (16/328) patients in the adalimumab group discontinued due to serious adverse events. In Study SC-IV, serious infections were reported in 3.8% (12/318) of patients treated with abatacept SC weekly, none which led to discontinuation, and in 5.8% (19/328) of patients treated with adalimumab SC every-other-week, leading to 9 discontinuations in the 24-month period.

Autoimmune disorders, mild to moderate in severity, were reported in 3.8% (12/318) patients in the SC abatacept group and 1.5% (5/328) patients in the adalimumab group over the 24-month period.

Summary of the safety profile in Psoriatic Arthritis (PsA)

ORENCIA has been studied in patients with active PsA in two placebo-controlled clinical trials (341 patients with ORENCIA, 253 patients with placebo) (see 5.1 Pharmacodynamic Properties - Clinical Trials). During the 24-week placebo-controlled period in the larger study PsA-II, the proportion of patients with adverse reactions was similar in the ORENCIA and placebo treatment groups (15.5% and 11.4%, respectively). There were no adverse reactions that occurred at ≥ 2% in either treatment group during the 24-week placebo-controlled period. The overall safety profile was comparable between studies PsA-I and PsA-II and consistent with the safety profile in rheumatoid arthritis.

Clinical trial experience in Juvenile Idiopathic Arthritis (JIA) patients treated with intravenous ORENCIA

In general, the adverse events in paediatric patients were similar in frequency and type to those seen in adult patients (see section 4.4 and 4.8).

ORENCIA has been studied in 190 paediatric patients, 6 to 17 years of age, with polyarticular JIA (see section 5.1). Overall frequency of adverse events in the 4-month, lead-in, open-label period of the study was 70%; infections occurred at a frequency of 36%. The most common infections were upper respiratory tract infection and nasopharyngitis. The infections resolved without sequelae, and the types of infections were consistent with those commonly seen in outpatient paediatric populations. Other events that occurred at a prevalence of at least 5% were headache, nausea, diarrheoa, cough, pyrexia, and abdominal pain.

A total of 6 serious adverse events (acute lymphocytic leukaemia, ovarian cyst, varicella infection, disease flare [2], and joint wear) were reported during the initial 4 months of treatment with ORENCIA.

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 (haematoma in one patient, varicella and encephalitis in the other).

Of the 190 patients with JIA treated with ORENCIA in this study, one (0.5%) patient discontinued due to non-consecutive infusion reactions, consisting of bronchospasm and urticaria. During Periods A, B, and C, acute infusion-related reactions occurred at a frequency of 4%, 2%, and 3%, respectively, and were consistent with the types of events reported in adults.

Upon continued treatment in the open-label extension period, 27.5% (42/153) of patients discontinued treatment, and the types of adverse events were similar in frequency and type to those seen in adult patients, except for a single 14 year old patient diagnosed with temporal lobe epilepsy secondary to multiple sclerosis (MS) while on open-label treatment. The subject was reported to have a probable seizure four days after the 12th infusion of abatacept. The subject had no known personal or family history of MS prior to study entry. This has been the only case of MS in the JIA study with abatacept and there is no evidence to date that there is an increased risk of MS or other demyelinating events due to abatacept treatment.

Adverse events regardless of causality occurring in ≥5% of paediatric patients receiving ORENCIA in Period B (double-blind phase) of the three part study conducted in paediatric and adolescent patients with polyarticular JIA are listed in Table 4 below by system organ classification. All adverse events listed below fall into the frequency category of common (≥1% - <10%), as defined above for adult RA.

Table 4: Adverse Events in Placebo-Controlled Trials (regardless of causality) at ≥ 5% for Period B (double-blind phase)

System Organ Classification / Preferred Term	ORENCIA n (%)	Placebo[a] n (%)
Number treated	60 (100)	62 (100)
Infections and infestations		
Influenza	5 (8.3)	4 (6.5)
Bacteriuria	4 (6.7)	0
Nasopharyngitis	4 (6.7)	3 (4.8)
Upper respiratory tract infection	4 (6.7)	5 (8.1)
Gastroenteritis	3 (5.0)	1 (1.6)
Sinusitis	3 (5.0)	2 (3.2)
Gastrointestinal disorders		
Abdominal pain	3 (5.0)	1 (1.6)
General disorders and administration site conditions		
Pyrexia	4 (6.7)	5 (8.1)
Nervous system disorders		
Headache	3 (5.0)	1 (1.6)

[a] Preceding the double-blind phase of the study (Period B), all patients were treated with ORENCIA for 4 months in the open-label, lead-in phase (Period A). At the conclusion of Period A, patients who exhibited a predefined clinical response were randomised into one of 2 arms (in Period B), and either continued on ORENCIA or withdrew from ORENCIA to receive placebo. See section 5.1 (Clinical trials in Juvenile Idiopathic Arthritis (JIA)).

Clinical Trial Adverse Drug Reactions (<5%)

ADRs reported in less than 5% for Period B (double-blind) for patients receiving ORENCIA in the paediatric clinical trials are listed below by body system.

Infections and Infestations: Sinusitis, influenza, rhinitis, tinea versicolour, upper respiratory tract infection, bacteriuria, otitis externa

Gastrointestinal disorders: Abdominal pain, nausea, aphthous stomatitis

Skin and subcutaneous tissue disorders: Pityriasis, skin lesion

Nervous system disorders: Headache

Renal and urinary disorders: Leukocyturia

Vascular disorders: Hypotension

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 paediatric clinical trial, 10.6% of ORENCIA treated patients that had negative antinuclear antibody titres at baseline had positive titres at Day 113. In Period B, 5.9% of ORENCIA-treated patients and 4.0% of placebo patients that had negative antinuclear antibody titres at baseline had positive titres 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 patients with polyarticular JIA following repeated treatment with ORENCIA. The rate of seropositivity while patients were receiving abatacept therapy was 0.5% (1/189) during Period A; 13.0% (7/54) during Period B; and 11.4% (17/149) during Period C. For patients in Period B who were randomised to placebo (therefore withdrawn from therapy for up to 6 months) the rate of seropositivity was 40.7% (22/54). Anti-abatacept antibodies were generally transient and of low titre. The absence of concomitant MTX did not appear to be associated with a higher rate of seropositivity in Period B placebo recipients. The presence of antibodies was not associated with adverse reactions or infusional reactions, or with changes in efficacy or serum abatacept concentrations. Of the 54 patients withdrawn from ORENCIA during the double-blind period for up to 6 months, none had an infusion reaction upon re-initiation of ORENCIA.

Malignancies

A single case of acute lymphocytic leukaemia was reported in the paediatric 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 was 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 (e.g. pruritus, throat tightness, dyspnoea) have been received following the use of SC ORENCIA.

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

Laboratory findings

Based on the results of clinical studies, no special laboratory evaluations are necessary in addition to careful medical management and supervision of patients.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: selective immunosuppressants, ATC code: L04AA24.

Actions

Abatacept is a costimulation modulator of the interaction of CD80 and CD86 on antigen presenting cells with CD28 on T-lymphocytes. Abatacept is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to the modified Fc (hinge, CH2, and CH3 domains) portion of human immunoglobulin G1. Abatacept is produced by recombinant DNA technology in Chinese hamster ovary cells. The apparent molecular weight of abatacept is 92 kilodaltons.

Abatacept modulates a key costimulatory signal required for full activation of T lymphocytes expressing CD28. T lymphocytes are found in the synovium of patients with RA. Activated T lymphocytes contribute to the pathogenesis of RA 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, costimulatory signal. A major costimulatory 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 inhibiting this costimulatory pathway. Studies indicate that abatacept affects both memory and naïve 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 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.

Dose finding studies were conducted with abatacept monotherapy (placebo, 0.5 mg/kg, 2 mg/kg, and 10 mg/kg) and in combination with MTX (placebo, 2 mg/kg, and 10 mg/kg). In both studies, the American College of Rheumatology (ACR) 20 response rate increased with increasing doses at 2mg/kg and 10 mg/kg. In clinical trials with ORENCIA using doses approximating 10mg/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, 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 this selective costimulation modulator.

CLINICAL TRIALS

Clinical trials in adult Rheumatoid Arthritis (RA) patients treated with intravenous ORENCIA

The efficacy and safety of ORENCIA for IV administration were assessed in six randomised, double-blind, placebo-controlled studies in patients ≥age 18 with active RA diagnosed according to American College of Rheumatology (ACR) criteria. The trials are designated as follows: Study I (IM103002), Study II (IM101100), Study III (IM101102, AIM), Study IV (IM101029, ATTAIN), and Study V (IM101031, ASSURE) and Study VI (IM101023, AGREE). Studies I, II, III, IV, and VI required patients to have at least 12 tender and 10 swollen joints at randomisation. Study V did not require any specific number of tender or swollen joints. ORENCIA or placebo treatment was given intravenously at weeks 0, 2, and 4 and then every 4 weeks thereafter.

Study I, a supportive study, evaluated ORENCIA as monotherapy in 122 patients with active RA who had failed at least one non-biologic DMARD or etanercept. In Study II and Study III, the efficacy and safety of ORENCIA were assessed in patients with an inadequate response to MTX and who were continued on their stable dose of MTX. In Study IV, the efficacy and safety of ORENCIA were assessed in patients with an inadequate response to a TNF blocking agent, with the TNF blocking agent discontinued prior to randomisation; other DMARDs were permitted. Study V primarily assessed safety in patients with active RA requiring additional intervention in spite of current therapy with DMARDs; all DMARDs used at enrolment were continued.

In Study VI, the efficacy and safety of ORENCIA were assessed in MTX-naive patients with early (≤2 years disease duration), severe active (tender joint count of at least 12, swollen joint count of at least 10, and a CRP of ≥ 0.45 mg/dL) erosive (erosion of the hands, wrists, or feet on radiograph) RA. In Study VI, patients previously naive to MTX were randomised to receive ORENCIA+MTX or MTX+placebo.

Study I patients were randomised to receive one of three doses of ORENCIA (0.5, 2, or 10 mg/kg) or placebo ending at Week 8. Study II patients were randomised to receive ORENCIA2 or 10 mg/kg or placebo for 12 months. For Studies I and II, only results in the 10mg/kg group are discussed below. Studies III, IV, V, and VI patients were randomised to receive a fixed dose approximating 10 mg/kg of ORENCIA or placebo for 12 months (Studies III, V, and VI) or 6 months (Study IV). The dose of ORENCIA was 500 mg for patients weighing less than 60 kg, 750 mg for patients weighing 60 to 100 kg, and 1 gram for patients weighing greater than 100 kg.

Clinical response

ACR response

The percent of ORENCIA-treated patients achieving ACR 20, 50, and 70 responses and major clinical response (defined as achieving an ACR 70 response for a continuous 6-month period) in Studies III, IV, and VI are shown in Table 5 Month 6 and 12 ACR response rates in Study II for the 10 mg/kg group were similar to the ORENCIA group in Study III. ACR response rates at 3 months in Study I were supportive of these findings.

In Studies III and IV, improvement in the ACR 20 response rate versus placebo was observed after administration of the first dose, as measured at Day 15, and was maintained through the double-blind study period. In Study VI, improvement in the ACR 20 response rate in ORENCIA+MTX-treated patients versus MTX+placebo-treated patients was observed at 29 days, and was maintained through the double-blind study period. The ACR 50 response with ORENCIA was significantly greater than placebo at Months 2 and 3, respectively, for Studies III and IV, with continued improvement in the ACR 50 response rate through the double-blind period (Month 12 in Study III and Month 6 in Study IV). In the placebo-controlled periods of Studies II, III, and VI ACR response rates were maintained to 12 months in ORENCIA-treated patients. In the uncontrolled open-label long-term extension of Studies II, III, IV, and VI, durable and sustained ACR 20, 50, and 70 responses have been observed through 7 years, 5 years, 5 years, and 2 years, respectively, of ORENCIA treatment based on as-observed analyses.

In Study II, ACR responses were assessed at 7 years with 31/43 (72%) ACR 20 responses, 25/43 (58%) ACR 50 responses, and 19/43 (44%) ACR 70 responses. In Study III, ACR responses were assessed at 5 years with 224/268 (84%) ACR 20 responses, 165/270 (61%) ACR 50 responses, and 107/270 (40%) ACR 70 responses. In Study IV, ACR responses were assessed at 5 years with 66/89 (74%) ACR 20 responses, 45/88 (51%) ACR 50 responses, and 21/ 91 (23%) ACR 70 responses. In Study VI, ACR responses were assessed at 2 years with 196/219 (90%) ACR 20 responses, 169/217 (78%) ACR 50 responses, and 124/216 (57%) ACR 70 responses.

Greater improvement was seen in all ACR response criteria components in ORENCIA-treated patients than in placebo-treated patients through 6 (Study IV) and 12 (Studies II and III) months. In Study VI, greater improvement was seen in all ACR components at 12 months in ORENCIA+MTX-treated patients than in MTX+placebo-treated patients. In the open-label extension of Studies II, III, and IV, improvements in the individual ACR components were maintained through 7, 5, and 5 years, respectively, of ORENCIA treatment.

Table 5: Clinical Responses in Controlled Trials

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

* p<0.05, ORENCIA vs placebo or ORENCIA+MTX vs MTX+placebo (Study VI).
** p<0.01, ORENCIA vs placebo or ORENCIA+MTX vs MTX+placebo (Study VI).
*** p<0.001, ORENCIA vs placebo or ORENCIA+MTX vs MTX+placebo (Study VI).
§ 95% CI: −4.2, 4.8 (based on prespecified margin for non-inferiority of −7.5%)
[a] Fixed dose approximating 10 mg/kg.
[b] Concurrent DMARDs included one or more of the following: MTX, azathioprine, chloroquine/hydroxychloroquine, gold, leflunomide, sulfasalazine, and anakinra.
[c] Major clinical response is defined as achieving an ACR 70 response for a continuous 6-month period
[d] DAS28-CRP Remission is defined as a DAS28-CRP score <2.6
[e] Per protocol data is presented in table. For ITT; n=736, 721 for SC and IV ORENCIA, respectively

Among ORENCIA-treated patients in Study III, 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 Study III, for patients treated with ORENCIA over two years including double-blind and open-label periods, the percentage of subjects achieving a major clinical response and an extended major clinical response increased to 34.3% and 24.5%, respectively.

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

DAS28 remission

Disease activity was also assessed using the Disease Activity Score 28 (DAS28). In Studies III and IV, the baseline mean DAS28 was 6.8 and 6.9 units, respectively, representing a high degree of disease activity. In Study III, the mean improvement in DAS28 at 12 months in ORENCIA-treated patients of 2.9 was significantly greater than the mean improvement of 1.5 observed in placebo-treated patients. DAS28 defined remission was achieved in 17% of ORENCIA-treated patients compared to 2% of placebo-treated patients at 12 months.

In Study IV, at Month 6, a significantly greater improvement in DAS28 was observed in the ORENCIA-treated patients than in placebo-treated patients (reduction of 2.0 vs. 0.7 units respectively, DAS28-defined remission was achieved in 10% of ORENCIA-treated patients compared to 1% of placebo-treated patients at 6 months.

In Study VI, patients treated with ORENCIA+MTX had a higher DAS28-CRP remission rate at 12 months than those treated with MTX+placebo (Table 5). Of patients treated with ORENCIA+MTX who achieved DAS28-CRP remission, 54% had no active joints, 17% had one active joint, 7% had two active joints, and 22% had three or more active joints, where an active joint was a joint that was rated as tender or swollen or both.

Radiographic response

Structural joint damage was assessed radiographically over a two-year period in Study III in RA patients with inadequate response to MTX. The results were measured using the Genant-modified Total Sharp score (TSS) and its components, the erosion score and Joint Space Narrowing (JSN) score. The baseline median TSS was 31.7 in ORENCIA-treated patients and 33.4 in placebo-treated patients. In the first year, patients received ORENCIA or placebo in double-blind fashion. ORENCIA+MTX inhibited the progression of structural damage compared to MTX+placebo after 12 months of treatment as shown in Table 6.

Inhibition of progression of structural damage with ORENCIA was observed regardless of disease duration (less than 2 years, 2 to 5 years, 5 to 10 years, and greater than 10 years).

Table 6: Mean Radiographic Changes Over 12 Months in Study III

Parameter	ORENCIA+MTX n=391	Placebo+MTX n=195	P-value[a]
Total Sharp score	1.21	2.32	0.012
Erosion score	0.63	1.14	0.029
JSN score	0.58	1.18	0.009

[a] Based on non-parametric analysis.

In the open-label extension of Study III, 75% (n=324) of patients initially randomised to ORENCIA+MTX were evaluated radiographically by the TSS. Following 2 years of treatment with ORENCIA+MTX, inhibition of progression of structural damage was observed. Fifty (50) percent of the patients had no progression of structural damage as defined by a change in the TSS of zero or less at 2 years. Eighty-six (86) percent of patients with no radiographic progression after 1 year of treatment with ORENCIA+MTX, had no progression at 2 years. For patients treated with ORENCIA+MTX, the mean change in TSS from Year 1 to Year 2 was 57% lower than the mean change in TSS from baseline to Year 1.

Based on year-to-year assessment, a decrease in radiographic progression was observed for all 3 scores with the most decrease observed in the first year of the abatacept treatment in the uncontrolled, open-label, long-term (LT) period. At the end of the LT period (4 years, Day 1821), 106/235 (45.1%) subjects in the original abatacept group and 45/115 (39.1%) subjects in the original placebo group showed no radiographic progression based on the Total score.

In Study VI, the mean change in TSS at 12 months was significantly lower in patients treated with ORENCIA+MTX compared to those treated with MTX+placebo. At 12 months 61% (148/242) of the patients treated with abatacept+MTX and 53% (128/242) of the patients treated with MTX+placebo had no progression (change from baseline in TSS ≤ 0). Among the patients who entered the open-label 12-month period, the progression of structural damage was lower in those receiving continuous abatacept+MTX treatment (for 24 months) compared to patients who initially received MTX+placebo (for 12 months) and were switched to abatacept+MTX for the next 12 months. Of these patients, 57% (121/213) who received continuous abatacept+MTX treatment and 44% (84/192) of patients who initially received MTX and switched to combination with abatacept had no progression.

The effect of ORENCIA on structural damage was not studied in RA patients with an inadequate response to TNF blocking agents.

Physical function response

Improvement in physical function was measured by the Health Assessment Questionnaire Disability Index (HAQ-DI) in Studies III, IV, and V, and a modified HAQ-DI in Study II. In Studies II-V, ORENCIA demonstrated significantly greater improvement from baseline than placebo in the HAQ-DI and a significantly greater proportion of patients treated with ORENCIA compared to placebo showed a clinically meaningful improvement (reduction in HAQ-DI of ≥0.3 units from baseline). In Study VI, significantly greater improvement from baseline in the HAQ-DI was observed in ORENCIA+MTX-treated patients compared with MTX+placebo-treated patients, and significantly more patients in the ORENCIA+MTX group compared with the MTX+placebo group achieved a clinically meaningful improvement at 12 months. In Study III, among HAQ responders at Month 12, 88% retained the response at Month 18, and 85% retained the response at Month 24. The results from Studies II-IV are shown in Table 7. During the open-label periods of Studies II, III, IV, and VI, the improvement in physical function has been maintained through 7 years, 5 years, 5 years, and 2 years, respectively.

Table 7: Mean Improvement from Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI)

	Inadequate Response to Methotrexate (MTX)				**Inadequate Response to TNF Blocking Agent**	
	Study II		**Study III**		**Study IV**	
HAQ Disability Index	ORENCIA[a] +MTX	Placebo +MTX	ORENCIA[b] +MTX	Placebo +MTX	ORENCIA[b] +DMARDs[c]	Placebo +DMARDs[c]
Baseline (Mean)	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,***] (n=113)	0.19[d] (n=118)	0.59[e,***] (n=420)	0.40[e] (n=211)	0.45[e,***] (n=249)	0.11[e] (n=130)
Month 12	0.40[d,***] (n=115)	0.15[d] (n=119)	0.66[e,***] (n=422)	0.37[e] (n=212)	NA	NA
Proportion of patients with a clinically meaningful improvement[f]						
Month 6	47%[d,**]	28%[d]	61%[e,***]	45%[e]	47%[e,***]	23%[e]
Month 12	38%[d,**]	20%[d]	64%[e,***]	39%[e]	NA	NA

** p<0.01, ORENCIA vs. placebo.
*** p<0.001, ORENCIA vs. placebo.

[a] 10 mg/kg.
[b] Fixed dose approximating 10 mg/kg
[c] Concurrent DMARDs included one or more of the following: MTX, azathioprine, chloroquine/hydroxychloroquine, gold, leflunomide, sulfasalazine, and anakinra.
[d] Modified Health Assessment Questionnaire; 0 = best, 3 = worst; 8 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.
[e] Health Assessment Questionnaire; 0 = best, 3 = worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.
[f] Reduction in HAQ-DI of ≥0.3 units from baseline.

Health-related outcomes and quality of life

Health-related quality of life was assessed by the SF-36 questionnaire at 6 months in Studies II, III, and IV and at 12 months in Studies II and III. In these studies, 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 (4 physical domains: physical function, role physical, bodily pain, general health; and 4 mental domains: vitality, social function, role emotional, mental health), as well as the Physical Component Summary (PCS) and the Mental Component Summary (MCS). In Study VI, improvement was observed at 12 months in the ORENCIA+MTX group as compared with the MTX+placebo group in both PCS and MCS and was maintained through 24 months.

In Studies III and IV, fatigue was measured by a validated Fatigue Visual Analogue Scale, and sleep problems were assessed by the Sleep Problems Index (SPI) of the Medical Outcomes Study Sleep Module. At 12 months and 6 months, in Study III and Study IV, respectively, statistically significant reductions in fatigue and sleep problems were observed in ORENCIA-treated patients as compared to placebo-treated patients. In open-label therapy with ORENCIA, improvements in health-related outcomes and quality of life have been maintained for up to 4 years.

Additional clinical trials in adult RA

Study VII: Abatacept or infliximab versus placebo

A randomised, double-blind study was conducted to assess the safety and efficacy of abatacept or infliximab versus placebo in patients with an inadequate response to MTX (Study VII, IM101043). Study VII patients received the same fixed dose of abatacept as that in Studies III-VI or 3 mg/kg infliximab or placebo for 6 months. Study VII continued for an additional 6 months with the abatacept and infliximab groups only. The primary outcome was the mean change in disease activity in abatacept-treated patients compared to placebo-treated patients at 6 months with a subsequent double-blind assessment of safety and efficacy of abatacept and infliximab at 12 months. The number of patients randomised was 156 to abatacept, 165 to infliximab, and 110 to placebo. In Study VII, the DAS28 mean changes from baseline at Months 6 and 12 are shown in Table 8, as are the percentages of patients achieving DAS28-defined low disease activity and remission. Greater improvement ($p \leq 0.001$) in DAS28 was observed with abatacept and with infliximab compared to placebo at six months in the placebo-controlled portion of the trial; the results between the abatacept and infliximab groups were similar. Further improvement was observed at 12 months with abatacept. The ACR responses in Study VII were consistent with the DAS28 score.

The open-label period of Study VII provided an assessment of the ability of abatacept to maintain efficacy for subjects originally randomised to abatacept and the efficacy response of those subjects who were switched to abatacept following treatment with infliximab. The reduction from baseline in mean DAS28 score at Day 365 (3.06) was maintained through Day 729 (3.34) in those patients who continued with abatacept. In those patients who initially received infliximab and then switched to abatacept, there was improvement in the mean DAS28 score at Day 729 (3.07) relative to day 365 (3.88).

At 6 months, the overall serious adverse events considered to be related to treatment was 1.9% (3 patients) in the abatacept group, 4.8% (8) in the infliximab group, and 2.7% (3) in the placebo group. The frequency of serious infections was 1.3% (2) in the abatacept group, 2.4% (4) in the infliximab group, and 0.9% (1) in the placebo group. The frequency of acute infusional adverse events was 5.1% (8) in the abatacept group, 18.2% (30) in the infliximab group, and 10.0% (11) in the placebo group. At

12 months, the overall serious adverse events considered to be related to treatment was 3.2% (5) in the abatacept group and 8.5% (14) in the infliximab group. The frequency of serious infections was 1.3% (2) in the abatacept group and 6.1% (10) in the infliximab group, with a total of 5 serious opportunistic infections in the infliximab group and none in the abatacept group. With regard to abnormal laboratory values at 6 months, antinuclear antibodies developed in 1.7% (2) of the abatacept group, 32.2% (38) of the infliximab group, and 4.9% (4) of the placebo group.

Table 8: Disease Activity Score 28 (DAS28 ESR) Results in Study VII

DAS28 Response	Abatacept+MTX n=150	Infliximab+MTX n=156	Placebo+MTX n=102
Mean Decrease			
Month 6	2.5 ***	2.3 ***	1.5
Month 12	2.9	2.3	NA[a]
Low Disease Activity			
Month 6	21%	26%	11%
Month 12	35%	22%	NA[a]
Remission			
Month 6	11%	13%	3%
Month 12	19%	12%	NA[a]

Note: Hypothesis tests performed only on the primary endpoint of DAS28 mean change at Month 6.
*** $p<0.001$ compared to placebo.
[a] Placebo administered for only 6 months.

Study VIII: Safety of abatacept in patients with or without washout of previous TNF blocking agent therapy

A study of open-label abatacept on a background of non-biologic DMARDs was conducted in patients with active RA who had an inadequate response to previous (washout for at least 2 months; n=449) or current (no washout period; n=597) TNF-antagonist therapy (Study VIII, IM101064). The primary outcome, incidence of adverse events, serious adverse events, and discontinuations due to adverse events during 6 months of treatment, was similar between those who were previous and current TNF-antagonist users at enrolment, as was the frequency of serious infections. Results from Study VIII support the transition from TNF blocking agent therapy to ORENCIA therapy at the next scheduled dose of the TNF blocking agent therapy.

Clinical trials in adult RA patients treated with subcutaneous ORENCIA

Study SC-I (IM101-174) was a randomised, double-blind, double-dummy non-inferiority study that compared the efficacy and safety of abatacept administered subcutaneously (with IV loading dose) to abatacept administered intravenously in subjects with RA, receiving background MTX as the only DMARD, and experiencing an inadequate response to MTX (MTX-IR). The primary endpoint was ACR 20 at 6 months. The pre-specified non-inferiority margin of -7.5% allows for a maximum difference in point estimate of -2.1% in the ACR 20 response of the SC ORENCIA compared with IV ORENCIA at Month 6, which is not considered a clinically significant difference**.** As shown in Table 5, the study demonstrated non-inferiority of ORENCIA administered subcutaneously vs intravenously with respect to ACR20 responses up to 6 months of treatment. The estimated difference between the 2 treatment groups (SC - IV) in the proportion of ACR 20 responders at Day 169 was 0.3% (95% CI: -4.2%, 4.8%). The proportion of subjects with an ACR 20 response at Day 169 was 76.0% in the SC abatacept group and 75.8% in the IV abatacept group (PP analysis).

In Study SC-1, patients were randomised with stratification by body weight (<60 kg, 60 to 100 kg, > 100 kg) to receive ORENCIA 125 mg SC injections weekly, after a single loading dose of ORENCIA based on body weight or ORENCIA intravenously on Days 1, 15, 29 and every four weeks thereafter.

A total of 2472 subjects were enrolled in Study SC-I; 1457 were treated, 736 of subjects with SC abatacept and 721 were with IV abatacept. Subjects continued taking their current dose of MTX from the day of randomisation.

Study SC-IV (IM101-235) was a randomised, investigator-blinded, non-inferiority study that compared the efficacy and safety of abatacept administered subcutaneously (without IV loading dose) to adalimumab administered subcutaneously in subjects with RA, receiving background MTX, and experiencing an inadequate response to MTX (MTX-IR).

The objective of Study SC-IV was to demonstrate non-inferiority of the efficacy and comparability of safety of SC ORENCIA relative to SC adalimumab in subjects with moderate to severely active RA and experiencing inadequate response to MTX.

In Study SC-IV, patients were randomised and stratified by disease severity (DAS28-CRP ≥3.2 and ≤5.1 and DAS28-CRP >5.1) to receive ORENCIA or adalimumab 40 mg SC injections every-other-week, both given in combination with MTX. Subjects continued taking their current dose of MTX from the day of randomisation.

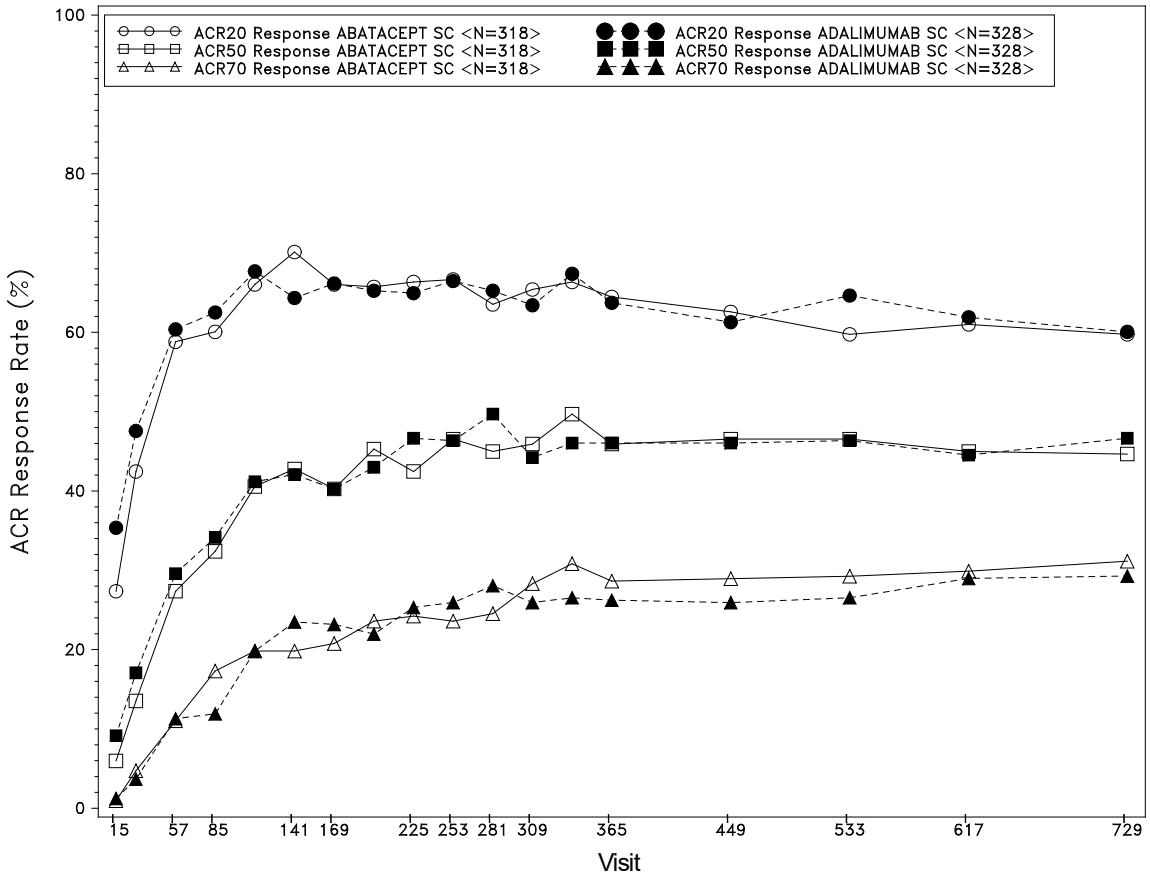
Clinical response

ACR Response

In Study SC-I, ORENCIA administered subcutaneously was non-inferior relative to IV infusions of ORENCIA with respect to ACR 20 responses up to 6 months of treatment. Patients treated with ORENCIA subcutaneously also achieved similar ACR 50 and 70 responses as those patients receiving ORENCIA intravenously at 6 months. No major differences in ACR responses were observed between IV and SC treatment groups in subgroups based on weight categories (less than 60 kg, 60 to 100 kg, and more than 100 kg; data not shown). The percent of ORENCIA-treated patients achieving ACR 20, 50, and 70 responses and major clinical response (defined as achieving an ACR 70 response for a continuous 6-month period) in Study SC-I are shown in Table 5.

In Study SC-IV the primary endpoint showed non-inferiority of ACR 20 response after 12 months of treatment, 64.8% (206/318) for the abatacept SC group and 63.4% (208/328) for the adalimumab SC group; treatment difference was 1.8% [95% confidence interval (CI): -5.6, 9.2] with comparable responses throughout the 24-month period. The respective values for ACR 20 at 24 months was 59.7% (190/318) for the abatacept SC group and 60.1% (197/328) for the adalimumab SC group. The respective values for ACR 50 and ACR 70 at 12 months and 24 months were consistent and similar for abatacept and adalimumab as shown in Figure 1.

Figure 1: ACR 20, ACR 50, and ACR 70 Response Over Time During 24 Month Period in Study SC-IV - All Randomised and Treated Subjects in 24 Month Period



DAS28 response

In Study SC-IV, the adjusted mean changes (standard error; SE) from baseline in DAS28-CRP were -2.35 (SE 0.08) [95% CI: -2.51, -2.19] and -2.33 (SE 0.08) [95% CI: -2.50, -2.17] in the SC abatacept group and the adalimumab group, respectively, at 24 months, with similar changes over time. The proportion of subjects achieving remission defined as a DAS28-CRP score of <2.6 was 50.6% (127/251) [95% CI: 44.4, 56.8] in the SC abatacept group and 53.3% (130/244) [95% CI: 47.0, 59.5] in the adalimumab group at 24 months.

Radiographic response

In Study SC-IV structural joint damage was assessed radiographically and expressed as a change from baseline using the van der Heijde-modified TSS and its components; the Erosion Score and JSN score as shown in Table 9. The proportion of subjects without radiographic progression in Total Score defined as a change from baseline ≤ smallest detectable change (SDC) (2.2) in the SC abatacept and adalimumab groups, respectively, at Month 12 was 87.8% (259/295) [95% CI: 84.1, 91.5] and 88.6% (263/297) [95% CI: 84.9, 92.2] and at Month 24 was 84.8% (218/257) [95% CI: 80.4, 89.2] and 83.8% (218/260) [95% CI: 79.4, 88.3]. Similar inhibition of radiographic damage was observed in both treatment groups up to 24 months.

Table 9: Mean Radiographic Change from Baseline (SD)[a] Over 12 and 24 Months in Study SC-IV

Parameter	Abatacept n=318	adalimumab n=328	Difference (CI)[b]
Total Sharp Score			
12 months	0.56 (2.62)	0.74 (6.57)	-0.19 (-0.99, 0.62)
24 months	0.89 (4.13)	1.13 (8.66)	-0.24 (-1.41, 0.93)
Erosion score			
12 months	0.21 (1.81)	0.25 (3.80)	-0.04 (-0.52, 0.44)
24 months	0.41 (2.57)	0.41 (5.04)	0.00 (-0.69, 0.69)
JSN score			
12 months	0.35 (1.67)	0.50 (3.03)	-0.14 (-0.54, 0.25)
24 months	0.48 (2.18)	0.72 (3.81)	-0.24 (-0.77, 0.30)

[a] SD = standard deviation
[b] Estimated treatment difference and 95% CI

Physical function response

In Study SC-IV, improvement from baseline as measured by HAQ-DI at 24 months and over time was similar between SC ORENCIA and adalimumab.

Health-related outcomes and quality of life

In Study SC-I, improvement from baseline as measured by HAQ-DI at 6 months and over time was similar between SC and IV administration.

Clinical trials in adult Psoriatic Arthritis (PsA)

The efficacy and safety of ORENCIA were assessed in two randomised, double-blind, placebo-controlled trials (Studies PsA-I and PsA-II) in adult patients, age 18 years and older. Patients had active PsA (≥ 3 swollen joints and ≥ 3 tender joints) despite prior treatment with DMARD therapy and had one qualifying psoriatic skin lesion of at least 2 cm in diameter.

In Study PsA-I, 170 patients received placebo or ORENCIA intravenously on Day 1, 15, 29, and then every 28 days thereafter in a double-blind manner for 24 weeks, followed by open-label ORENCIA 10 mg/kg IV every 28 days. Patients were randomised to receive placebo or ORENCIA 3 mg/kg, 10 mg/kg, or two doses of 30 mg/kg followed by 10 mg/kg, without escape for 24 weeks, followed by open label abatacept 10 mg/kg monthly IV every month. Patients were allowed to receive stable doses of concomitant MTX, low dose corticosteroids (equivalent to ≤ 10 mg of prednisone) and/or NSAIDs during the trial.

In Study PsA-II, 424 patients were randomised 1:1 to receive in a double-blind manner weekly doses of SC placebo or ORENCIA 125 mg without a loading dose for 24 weeks, followed by open-label ORENCIA 125 mg SC weekly. Patients were allowed to receive stable doses of concomitant MTX, sulfasalazine, leflunomide, hydroxychloroquine, low dose corticosteroids (equivalent to ≤ 10 mg of prednisone) and/or NSAIDs during the trial. Patients who had not achieved at least a 20% improvement from baseline in their swollen and tender joint counts by Week 16 escaped to open-label abatacept 125 mg SC weekly.

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

Clinical response

Signs and symptoms

The percent of patients achieving ACR 20, 50, or 70 responses at the recommended ORENCIA dose in Studies PsA-I (10 mg/kg IV) and PsA-II (125 mg SC) are presented in Table 10 below.

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

	PsA-I[a]			PsA-II[b,c]		
	Abatacept 10 mg/kg IV N=40	**Placebo N=42**	**Estimate of difference (95% CI)**	**Abatacept 125 mg SC N=213**	**Placebo N=211**	**Estimate of difference (95% CI)**
ACR 20	47.5%*	19.0%	28.7 (9.4, 48.0)	39.4%*	22.3%	17.2 (8.7, 25.6)
ACR 50	25.0%	2.4%	22.7 (8.6, 36.9)	19.2%	12.3%	6.9 (0.1, 13.7)
ACR 70	12.5%	0%	12.5 (2.3, 22.7)	10.3%	6.6%	3.7 (-1.5, 8.9)

* $p < 0.05$ vs placebo, p values not assessed for ACR 50 and ACR 70.
[a] 37% of patients were previously treated with TNF inhibitor.
[b] 61% of patients were previously treated with TNF inhibitor.
[c] Patients who had less than 20% improvement in tender or swollen joint counts at Week 16 met escape criteria and were considered non-responders.

A significantly higher proportion of patients achieved an ACR 20 response after treatment with ORENCIA 10 mg/kg IV or 125 mg SC compared to placebo at Week 24, regardless of prior TNF-inhibitor treatment. In Study PsA-I, the ACR 20 responses with ORENCIA 10 mg/kg IV vs placebo in patients who were TNF inhibitor-naive were 55.6% vs 20.0%, respectively, and in patients who were TNF inhibitor-experienced were 30.8% vs 16.7%, respectively. In Study PsA-II, the ACR 20 responses with ORENCIA 125 mg SC vs placebo in patients who were TNF inhibitor-naive were 44.0% vs 22.2%, respectively (21.9 [8.3, 35.6], estimate of difference [95% CI]), and in patients who were TNF inhibitor-experienced were 36.4% vs 22.3%, respectively, (14.0 [3.3, 24.8], estimate of difference [95% CI]).

Higher ACR 20 responses in Study PsA-II were seen with ORENCIA 125 mg SC vs. placebo irrespective of concomitant non-biologic DMARD treatment. The ACR 20 responses with ORENCIA 125 mg SC vs placebo in patients who did not use non-biologic DMARDs were 27.3% vs 12.1%, respectively, (15.15 [1.83, 28.47], estimate of difference [95% CI]), and in patients who did use non-biologic DMARDs were 44.9% vs 26.9%, respectively, (18.00 [7.20, 28.81], estimate of difference [95% CI]).

Consistent improvement was observed for each ACR component with abatacept treatment compared to placebo at Week 24 in Studies PsA-I and PsA-II.

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

Clinical responses were maintained or continued to improve up to one year in Studies PsA-I and PsA-II.

Structural response

In PsA-I, structural changes and musculoskeletal manifestations were evaluated by MRI. Mean improvements from baseline [SD] at Week 24 were numerically greater with ORENCIA 10 mg/kg IV vs placebo in erosions (-0.60 [4.23] vs 1.48 [7.37]), bone oedema (-1.12 [2.55] vs 0.44 [3.33]); synovitis (-1.40 [2.99] vs 0.81 [4.33]); dactylitis (-0.27 [0.70] vs -0.10 [0.51]), and enthesitis (-1.04 [1.51] vs 0.04 [1.29]), respectively.

In Study PsA-II, the proportion of radiographic non-progressors (≤ 0 change from baseline) in total PsA-modified SHS on x-rays at Week 24 was greater with ORENCIA 125 mg SC (42.7%) than placebo (32.7%), (10.0 [1.0, 19.1], estimate of difference [95% CI]). The progression of structural damage as assessed by mean change from baseline (95% CI) in PsA-modified SHS at Week 24 for ORENCIA versus placebo was 0.30 (0.06, 0.54) versus 0.35 (0.09, 0.60), and at Week 52 for ORENCIA versus placebo (which was followed by open-label ORENCIA) was 0.18 (-0.06, 0.42) versus 0.30 (0.06, 0.55), respectively.

Physical Function Response

In Study PsA-I, improvement in physical function with ORENCIA was seen in the proportion of patients with at least ≥ 0.30 decrease from baseline in HAQ-DI score, 45.0% with IV ORENCIA vs 19.0% with placebo (26.1 [6.8, 45.5], estimate of difference [95% CI]) at Week 24. In Study PsA-II, the proportion of patients with at least ≥ 0.35 decrease from baseline in HAQ-DI was 31.0% with ORENCIA vs. 23.7% with placebo (7.2 [-1.1, 15.6], estimate of difference [95% CI]), with a higher adjusted mean change from baseline in HAQ-DI with ORENCIA (-0.33) vs. placebo (-0.20) (-0.13 [-0.25, -0.01], estimate of difference [95% CI]) at Week 24. Improvement in HAQ-DI scores was maintained or improved for up to 1 year with continuing abatacept treatment in both PsA-I and PsA-II studies.

Clinical trials in Juvenile Idiopathic Arthritis (JIA)

The safety and efficacy of ORENCIA were assessed in a three-part study (IM101033, AWAKEN) including an open-label extension in children with polyarticular JIA. The study enrolled patients 6 to 17 years of age with moderately to severely active polyarticular JIA who had an inadequate response or intolerance to one or more DMARDs, such as MTX or TNF antagonists. Patients had a disease duration of approximately 4 years with 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%). Patients with systemic JIA who had intermittent fever, rheumatoid rash, hepatosplenomegaly, pleuritis, pericarditis or macrophage activation syndrome within the prior 6 months were excluded. At study entry, 74% of patients were receiving MTX (mean dose, 13.2 mg/m^2 per week) and remained on a stable dose of MTX (those not receiving MTX did not initiate MTX treatment during the study as this was not mandated as part of the protocol).

In Period A (open-label, lead-in), 190 patients (33% of whom were under 12 years of age), were treated with ORENCIA; patients received 10 mg/kg (maximum 1000 mg per dose) intravenously on Days 1, 15, 29, and monthly thereafter. Response was assessed utilising the ACR Paediatric30 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 randomised 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 either was 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, paediatric ACR 30/50/70 responses were 65%, 50%, and 28%, respectively. Paediatric ACR 30 responses were similar in all subtypes of JIA studied.

During the double-blind randomised 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 that for patients withdrawn from ORENCIA treatment (hazard ratio=0.31, 95% CI [0.16, 0.59]). Among patients who received ORENCIA throughout the study (Period A, Period B, and the open-label extension Period C), the proportion of paediatric ACR 30/50/70 responders has remained consistent for 31 months.

The Period C data from the JIA study indicates that efficacy measured by ACR 30, 50, and 70 response rate can occur later in subjects that were initially non-responders following 4 months of abatacept therapy. These data indicates that longer treatment duration may be necessary in some patients before the benefits of abatacept are observed. In both the biologic experienced and the non-biologic experienced non-responders subjects, an incremental benefit is observed following longer therapy with greater response being observed between Days 253 to Days 337 in Period C. Therefore an additional 6

to 9 months (total of 10 to 13 months) of abatacept treatment may be required to observe a benefit in those patients who were not initially responders to 4 months of therapy.

The selection of an optimal time frame to wait for a treatment response depends on a number of factors including weighing the potential benefits with that of the potential risks and the availability of alternative therapies since it is not appropriate to allow patients to experience prolonged symptoms while waiting for the effect of a therapeutic intervention.

The 6-months time frame was specified for the adult RA indication, and is proposed for the paediatric JIA indication. The available information is suggestive of more responses as treatment is extended beyond 4 months in JIA but the data may not be sufficient to specify a more precise and different recommendation between the adult and the JIA populations. Nonetheless, it is important to convey to the prescriber that additional responses may be observed with longer treatment in those patients who are initially non-responders. Based on the data the additional time frame should not exceed a total of 10 months.

There is no clinical trial data for the use of ORENCIA SC formulation in children, therefore its use in children cannot be recommended.

ORENCIA has not been studied in children less than 6 years of age. The long-term effects of ORENCIA therapy on skeletal, behavioural, cognitive, sexual, and immune maturation and development in children are unknown.

5.2 Pharmacokinetic properties

Healthy adults and adult RA – IV Infusion

Absorption

Abatacept is administered intravenously.

Distribution

The pharmacokinetics of abatacept were studied in healthy adult subjects after a single 10 mg/kg IV infusion and in RA patients after multiple 10 mg/kg IV infusions (see Table 11).

Table 11: Pharmacokinetic Parameters (Mean, Range) in Healthy Subjects and RA Patients After 10 mg/kg Intravenous Infusion(s)

PK Parameter	Healthy Subjects (After 10 mg/kg Single Dose) n=13	RA Patients (After 10 mg/kg Multiple Doses[a]) n=14
Peak Concentration (C_{max}) [mcg/mL]	292 (175-427)	295 (171-398)
Terminal half-life ($t_{1/2}$) [days]	16.7 (12-23)	13.1 (8-25)
Systemic clearance (CL) [mL/h/kg]	0.23 (0.16-0.30)	0.22 (0.13-0.47)
Volume of distribution (Vss) [L/kg]	0.09 (0.06-0.13)	0.07 (0.02-0.13)

[a] Multiple intravenous infusions were administered at Days 1, 15, 30, and monthly thereafter.

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

Population pharmacokinetic analyses in RA patients revealed that there was a trend toward higher clearance of abatacept with increasing body weight. Age and gender (when corrected for body weight)

did not affect clearance. Concomitant MTX, NSAIDs, corticosteroids, and TNF blocking agents did not influence abatacept clearance.

Adult RA - SC Administration

Absorption

Abatacept is administered subcutaneously.

Distribution

Abatacept exhibited linear pharmacokinetics following SC administration. The mean (range) for C_{min} and C_{max} at steady state observed after 85 days of treatment was 32.5 mcg/mL (6.6 to 113.8 mcg/mL) and 48.1 mcg/mL (9.8 to 132.4 mcg/mL), respectively. The bioavailability of abatacept following SC administration relative to IV administration 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.

A single study was conducted to determine the effect of monotherapy use of abatacept on immunogenicity following SC administration without an IV load. When the IV loading dose was not administered, a mean trough concentration of 12.6 mcg/mL was achieved after 2 weeks of dosing. The efficacy response over time in this study appeared consistent with studies that included an IV loading dose, however, the effect of no IV load on the onset of efficacy has not been formally studied.

Consistent with the IV data, population pharmacokinetic analyses for SC abatacept in RA patients revealed that there was a trend toward higher clearance of abatacept with increasing body weight. Age and gender (when corrected for body weight) did not affect apparent clearance. Concomitant MTX, NSAIDs, corticosteroids, and TNF blocking agents did not influence abatacept apparent clearance.

Adult PsA

In PsA-I, patients were randomised to receive IV placebo or abatacept 3 mg/kg (3/3 mg/kg), 10 mg/kg (10/10 mg/kg), or two doses of 30 mg/kg followed by 10 mg/kg (30/10 mg/kg), on Day 1, 15, 29, and then every 28 days thereafter. In this study, the steady-state concentrations of abatacept were dose-related. The geometric mean (CV%) C_{min} at Day 169 were 7.8 µg/mL (56.3%) for the 3/3 mg/kg, 24.3 µg/mL (40.8%) for 10/10 mg/kg, and 26.6 µg/mL (39.0%) for the 30/10 mg/kg regimens.

In Study PsA-II following weekly SC administration of abatacept at 125 mg, steady-state of abatacept was reached at Day 57 with the geometric mean (CV%) C_{min} ranging from 22.3 (54.2%) to 25.6 (47.7%) µg/mL on Days 57 to 169, respectively.

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

Metabolism

Studies were not carried out to evaluate the metabolism of abatacept in humans. Owing to steric and hydrophilic considerations, abatacept would not be metabolised by liver cytochrome P450 enzymes.

Excretion

Studies were not carried out to evaluate the elimination of abatacept in humans. Because of its large molecular weight abatacept is not expected to undergo renal elimination.

Special populations

Paediatric and adolescent patients.

Population pharmacokinetic analysis of abatacept serum concentration data from patients with JIA aged 6 to 17 years following administration of abatacept 10 mg/kg revealed that the estimated clearance of abatacept, when normalised for baseline body weight, was higher in JIA patients (0.44 mL/h/kg) versus adult RA patients. After accounting for the effect of body weight, the clearance of abatacept was not related to age or gender. Mean estimates for distribution volume and elimination half-life were 0.12 L/kg and 11.2 days, respectively. As a result of the higher body-weight normalised clearance in JIA patients, the predicted systemic exposure of abatacept was lower than that observed in adults, such that the observed mean (range) peak and trough concentrations were 217 (57 to 700) and 11.9 (0.15 to 44.6) mcg/mL, respectively. Administration of other concomitant medications such as MTX, corticosteroids, and NSAIDs did not influence the clearance of abatacept in JIA patients.

No formal studies were conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of abatacept. Thus, both the long-term safety and effectiveness of abatacept in children with renal or hepatic impairment are also unknown. The use of abatacept in this special population is not recommended.

5.3 Preclinical safety data

Pregnancy

Embryofetal development was unaffected by doses of up to 300 mg/kg/day in mice, 200 mg/kg/day in rats, and 200 mg/kg every 3 days in rabbits (approximately 29-fold the human drug exposure based on AUC). Abatacept was shown substantially to cross the placenta in rats, and minimally in rabbits. Offspring were unaffected by abatacept doses of up to 45 mg/kg given every 3 days to rats from early gestation through to the end of lactation (3-fold the human drug exposure based on AUC). With a dose of 200 mg/kg every 3 days (approximately 11-fold the human drug exposure based on AUC) female pups showed enhanced T cell dependent antibody responses and a single case (out of 20 pups) of thyroid chronic inflammation. Whether these findings indicate a potential for the development of autoimmune diseases in humans exposed *in utero* is uncertain.

Genotoxicity

Abatacept was not genotoxic in *in vitro* tests for reverse gene mutation in bacteria, forward gene mutation in mammalian cells, and clastogenicity in human lymphocytes.

Carcinogenicity

In a long-term carcinogenicity study in mice, weekly subcutaneous abatacept treatment for up to 84-88 weeks resulted in increased incidences of malignant lymphomas at all doses (0.8 to 3-fold the human drug exposure based on AUC). Increased incidences of female mammary gland tumours were also observed at drug exposures (AUC) 2 to 3-fold the human exposure. While these tumours may be related to activation of murine leukaemia virus and mouse mammary tumour virus, respectively, by prolonged immunosuppression, there is no conclusive evidence to support this hypothesis.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lyophilized powder for IV infusion

Maltose
Monobasic sodium phosphate
Sodium chloride

Solution for subcutaneous administration

Sucrose
Poloxamer
Monobasic sodium phosphate
Dibasic sodium phosphate
Water for injections

ORENCIA solution for subcutaneous administration contains no maltose.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicines.

6.3 Shelf life

Lyophilized powder for IV infusion

Unopened vial: 3 years

After dilution: To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary hold at 2 to 8 ºC for not more than 24 hours.

Solution for subcutaneous administration

Pre-filled syringe or autoinjector: 2 years

6.4 Special precautions for storage

Lyophilized powder for IV infusion

ORENCIA lyophilized powder must be refrigerated at 2°C to 8°C.

For storage conditions after dilution of the medicine see section 6.3.

Solution for subcutaneous administration

ORENCIA solution for subcutaneous administration must be refrigerated at 2°C to 8°C. DO NOT FREEZE.

Do not use beyond the expiration date.

Protect the vials, pre-filled syringes, and autoinjectors from light by storing in the original package until time of use.

6.5 Nature and contents of container

Lyophilized powder for IV infusion

ORENCIA is a lyophilized powder for intravenous infusion; it is supplied as an individually packaged, single-use vial with a silicone-free disposable syringe. The product is available in the strength of 250 mg of abatacept in a 15 mL vial.

Solution for subcutaneous administration

ORENCIA solution for subcutaneous administration is supplied either in a 1 mL single-dose disposable prefilled glass syringe with a passive needle safety guard, a 1 mL single-dose disposable prefilled glass syringe with flange extender, or a 1 mL single-dose disposable ClickJect® Prefilled Autoinjector. The product is available in the strength of 125 mg of abatacept and is provided in a pack of four 1 mL prefilled syringes or autoinjectors.

Not all presentations may be available.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Bristol-Myers Squibb (NZ) Limited
Private Bag 92518
Auckland 1141

Tel: Toll free 0800 167 567

9 DATE OF FIRST APPROVAL

Lyophilized powder for IV infusion

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Solution for subcutaneous administration

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DATE OF REVISION OF THE TEXT

07/01/2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4 Special warnings and precautions for use	Update on the use of non-live vaccines.
All	Editorial updates

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