

AUSTRALIAN PRODUCT INFORMATION – ORENCIA[®] (ABATACEPT)

1 NAME OF THE MEDICINE

ORENCIA (abatacept)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Lyophilized Powder for IV Infusion

Each vial contains 250 mg abatacept.

Excipient with known effect

Each vial contains 8.625 mg sodium.

Solution for Subcutaneous Administration

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

Excipient with known effect

Each syringe or autoinjector contains 0.322mg 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 as monotherapy or 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 RA or PsA, ORENCIA may be administered as an intravenous (IV) infusion or a subcutaneous (SC) injection. Methotrexate, 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 intravenous infusion utilizing the weight range-based dosing specified in Table 1. Following the initial IV administration, an intravenous 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 4.2 Dose and method of administration – Special Populations - Paediatric and adolescent).

Subcutaneous dosing regimen

Rheumatoid Arthritis

ORENCIA SC should be administered weekly at a dose of 125 mg by subcutaneous 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 intravenous infusion (based on body weight categories, see Table 1), followed by the first 125 mg subcutaneous injection administered within a day of the IV infusion.

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

Psoriatic Arthritis

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

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

Hypersensitivity Reactions

Hypersensitivity reactions are uncommon with the infusion of ORENCIA, however these may occur. To minimize the incidence of hypersensitivity reactions, the patient should be monitored closely before and after ORENCIA administration. Should any such reaction occur, then appropriate responses and treatments are to be initiated. The necessary equipment, treatments and procedures sufficient to initiate management of acute infusion reactions (anaphylaxis) should be in place.

The risk of hypersensitivity reactions including anaphylaxis and how they are managed should be discussed with the patient by the prescriber prior to the patient receiving ORENCIA, so that the patient is aware of such risks and has an understanding of these risks.

SPECIAL POPULATIONS

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 intravenous infusion. Following the initial administration, ORENCIA should be given at 2 and 4 weeks after the first infusion and every 4 weeks thereafter. Any unused portions in the vials must be immediately discarded.

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

Elderly patients

No dose adjustment is required (see 4.4 Special Warnings and Precautions for Use).

Patients with renal impairment or hepatic impairment

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

Concomitant therapy

Methotrexate, other non-biologic DMARDs, corticosteroids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics may be used during treatment with ORENCIA.

METHOD OF ADMINISTRATION

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 – 8°C 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 ONLY 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 center 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 minimize 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 intravenous 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.

If the **SILICONE-FREE DISPOSABLE SYRINGE** is dropped or becomes contaminated, use a new **SILICONE-FREE DISPOSABLE SYRINGE** from inventory. For information on obtaining additional **SILICONE-FREE DISPOSABLE SYRINGES**, contact Bristol-Myers Squibb Australia 1800-RENCIA or contact Bristol-Myers Squibb Australia 1800-067567.

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 section 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 subcutaneous administration should be instructed to inject the full amount in the syringe or autoinjector (1.0 mL), which provides 125 mg of ORENCIA, according to the directions provided in the Patient/Caregiver Instructions for Use section.

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

4.3 CONTRAINDICATIONS

ORENCIA should not be administered to patients with known hypersensitivity to ORENCIA or any of its components (see 2 Qualitative and Quantitative Composition and 6.1 List of Excipients). 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 intravenous 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 intravenous administration in clinical trials, where patients were not required to be pretreated to prevent hypersensitivity reactions. The occurrence of anaphylaxis remained rare between the double blind trials and long-term open-label experience (see 4.8 Adverse Effects (Undesirable Effects) - Infusion-related reactions and hypersensitivity reactions). 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. 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.

In a small study with healthy subjects ORENCIA reduced the quantitative immune response (measured via antibody titer against the tetanus toxoid vaccine and pneumococci antigens). However the 2-fold increase in titer response to these antigens was not altered.

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 localized infections. Patients who develop a new infection while undergoing treatment with ORENCIA should be monitored closely. Administration of ORENCIA should be discontinued if a patient develops a serious infection. 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, of 1955 ORENCIA patients and 989 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.

Malignancies

In the placebo-controlled clinical trials in adult RA, the frequencies of malignancies in abatacept- and placebo-treated patients were 1.4% and 1.1%, respectively (see 4.8 Adverse Effects (Undesirable Effects)). 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 5.3 Preclinical Safety Data - Carcinogenicity). 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 4.8 Adverse Effects (Undesirable Effects)). Periodic skin examination is recommended for all patients, particularly for those with risk factors for skin cancer.

Infusion-related 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 pretreated to prevent hypersensitivity reactions (see 4.8 Adverse Effects (Undesirable Effects) - Infusion-related reactions and hypersensitivity reactions).

Immunizations

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. No data are available on the effects of vaccinations in patients receiving ORENCIA. Drugs that affect the immune system, including ORENCIA, may blunt the effectiveness of some immunizations.

It is recommended that patients with juvenile idiopathic arthritis be brought up to date with all immunizations in agreement with current immunization 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.

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 4.2 Dose and Method of Administration - Preparation and Administration Instructions for Subcutaneous Injection).

Information for Patients

Patients should be provided the ORENCIA Patient Information leaflet and 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 Patient Information be discussed.

Use in the elderly

A total of 323 patients 65 years of age and older, including 53 patients 75 years and older, received ORENCIA in 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.

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 disease-modifying anti-rheumatic drugs (DMARDs). ORENCIA may be used as monotherapy or concomitantly with methotrexate (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 subcutaneous 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.

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 intravenous 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 nicotinic adenine dinucleotide (GDH-NAD), glucose oxidase, or glucose hexokinase test methods.

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 5.2 Pharmacokinetic Properties).

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

Effects on 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).

Use in 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 fetus. (See 5.3 Preclinical safety data)

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 5 months following the mother's last exposure to abatacept during pregnancy. Please refer to the Product Information of the vaccine being considered to confirm it is not a live vaccine.

Use in lactation

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.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trial experience in adult RA patients treated with intravenous ORENCIA

ORENCIA has been studied in patients with active rheumatoid arthritis in placebo-controlled clinical trials (1955 patients with ORENCIA, 989 with placebo). The trials had either a double-blind, placebo-controlled period of 6 months (258 patients with ORENCIA, 133 with placebo) or 1 year (1697 patients with ORENCIA, 856 with placebo). Most patients in these trials were taking methotrexate (81.9% with ORENCIA, 83.3% with placebo). Other concomitant medications included: NSAIDs (83.9% with ORENCIA, 85.1% with placebo); systemic corticosteroids (74.7% with ORENCIA, 75.8% with placebo); non-biological DMARD therapy, most commonly chloroquine/hydroxychloroquine, leflunomide and/or sulfasalazine (26.9% with ORENCIA, 32.1% with placebo); TNF blocking agents, mainly etanercept (9.4% with ORENCIA, 12.3% with placebo); and anakinra (1.1% with ORENCIA, 1.6% 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 52.2% of ORENCIA-treated patients and 46.1% of placebo-treated patients. The most frequently reported adverse drug reactions ($\geq 5\%$) among ORENCIA-treated patients were headache and nausea. The proportion of patients who discontinued treatment due to ADRs was 3.4% for ORENCIA-treated patients and 2.2% 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 Rheumatoid Arthritis Patients

	ORENCIA (n=1955) Percentage	Placebo (n=989) Percentage
All adverse events	88.8	85.1
Serious adverse events	14.0	12.5
Infections and infestations	54.1	48.7
Malignancies	1.4	1.1
Acute infusion-related events (reported within 1 hour of the start of the infusion)	9.8	6.7

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
Study IV, Inadequate Response to TNF Blocking Agent				
ORENCIA	61.2%	47.3%	8.1%	1.9%

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

	Percent of Patients			
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 rheumatoid arthritis.

Adverse drug reactions greater in frequency (difference >0.2%) in ORENCIA-treated patients compared to placebo patients are listed below by system organ class and frequency (very common ³ 10%; common ³ 1% - <10%; uncommon ³ 0.1% - <1%; rare ³ 0.01% - <0.1%).

Infections and infestations

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

Neoplasms benign and malignant (including cysts and polyps)

- Uncommon: Basal cell carcinoma

Blood and the lymphatic system disorders

- Common: Leukopenia
- Uncommon: Thrombocytopenia

Psychiatric disorders

- Uncommon: Depression, anxiety, sleep disorder (including insomnia)

Nervous system disorders

- Common: Headache, dizziness, paraesthesia

Eye disorders

- Common: Conjunctivitis
- Uncommon: Visual acuity reduced

Ear and labyrinth disorders

- Uncommon: Vertigo

Cardiac disorders

- Uncommon: Tachycardia, bradycardia, palpitations

Vascular disorders

- Common: Hypertension, flushing

Uncommon:	Hypotension, hot flush
<i>Respiratory, thoracic and mediastinal disorders</i>	
Common:	Cough
<i>Gastrointestinal disorders</i>	
Common:	Abdominal pain, diarrhoea, nausea, dyspepsia, mouth ulceration, aphthous stomatitis
Uncommon:	Gastritis
<i>Skin and subcutaneous tissue disorders</i>	
Common:	Rash (including dermatitis), alopecia
Uncommon:	Increased tendency to bruise, dry skin, hyperhidrosis, erythema
<i>Musculoskeletal, connective tissue and bone disorders</i>	
Common:	Pain in extremity
Uncommon:	Arthralgia
<i>Reproductive system and breast disorders</i>	
Uncommon:	Amenorrhea, menorrhagia
<i>General disorders and administration site conditions</i>	
Common:	Fatigue, asthenia
Uncommon:	Influenza-like illness
<i>Investigations</i>	
Common:	Blood pressure increased, liver function test abnormal (including transaminases increased)
Uncommon:	Blood pressure decreased, weight increased

Infections

In the placebo-controlled trials, infections at least possibly related to treatment were reported in 23.2% of ORENCIA-treated patients and 19.5% of placebo patients.

AEs reported in patients treated by abatacept intravenous or subcutaneous 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 1.8% of ORENCIA-treated patients and 1.0% of placebo patients. The most frequent (0.1-0.3%) serious infections at least possibly related to treatment reported with ORENCIA were pneumonia, cellulitis, localized infection, urinary tract infection, bronchitis, diverticulitis, and acute pyelonephritis (see 4.4 Special Warnings and Precautions for Use).

In double-blind and open-label clinical trials in 4,149 patients treated with abatacept during 11,658 patient-years, the incidence rate of serious infections was 2.87 per 100 patient-years, and the annualized incidence rate remained stable.

Malignancies

In placebo-controlled clinical trials, malignancies were reported in 27 of 1955 ORENCIA-treated patients observed during 1687 patient-years, and in 11 of 989 placebo-treated patients observed during 794 patient-years.

In double-blind and open-label clinical trials in 4,149 patients treated with ORENCIA during 11,658 patient-years, (of which over 1,000 were treated with abatacept for over 5 years), the incidence rate of malignancy was 1.41 per 100 patient-years, and the annualised incidence rate remained stable. The incidence rates per 100 patient-years were 0.74 for non-melanomatous skin cancer, 0.57 for solid malignancies and 0.13 for hematologic malignancies. The most frequently reported solid organ cancer was lung cancer (0.15 per 100 patient-years), and the most common hematologic malignancy was lymphoma (0.07 per 100 patient-years). The incidence rate did not increase for malignancies overall, by major type (non-melanomatous skin cancer, solid tumors, and hematologic malignancies), or for individual tumor types in the double-blind and open-label period compared to the double-blind experience. The type and pattern of malignancies reported during the open-label period of the trials were similar to those reported for the double-blind experience.

The incidence rate of observed malignancies was consistent with that expected in an age- and gender-matched rheumatoid arthritis population.

With regard to the general population, the observed and expected malignancies and the standardised incidence ratios are shown in Table 4.

Table 4: Observed and Expected Malignancies and Standardised Incidence Ratios (SIRs) Compared with the General Population^a

Malignancy	Observed ^b	Expected ^c	SIR (95% CI) ^d
Overall Solid Organ Malignancies	28	37.25	0.75 (0.50, 1.09)
Lung	11	4.88	2.25 (1.12, 4.03)
Breast	4	9.66	0.41 (0.11, 1.10)
Prostate	3	3.92	0.77 (0.15, 2.24)
Colon/Rectum	0	3.54	0 (0.00, 1.04)
Lymphoma	4	1.34	3.00 (0.81, 7.67)

^a General Population Rate estimates from United States Surveillance and End Results (SEER).

^b Observed number in ORENCIA-exposed patients in double-blind and open-label clinical trials.

^c Based on General Population (SEER) rate estimates; adjusted for age and gender and takes into account duration of ORENCIA exposure.

^d SIR -Standardised incidence ratio (Observed/Expected) 95% CI - confidence interval.

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 pretreated to prevent hypersensitivity reactions.

Acute infusion reactions (within 1 hour of infusion) the incidence rate of 4.04 per 100 p-y. 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 p-y were dizziness (0.70), headache (0.69),

hypertension (0.62), and nausea (0.40). The frequencies of these 4 events were 1.9%, 1.8%, 1.7%, and 1.1%, respectively. Greater than 95% of all subjects with acute-infusional events were mild or moderate in intensity.

Peri-infusion reactions (up to 24 hours after infusion) the incidence rate was 11.63 per 100 p-y. The 4 most common events contributing to this overall incidence rate per 100 p-y were headache (3.09), nausea (1.69), dizziness (1.56), and hypertension (1.16). Approximately 95% of all subjects with peri-infusional events had events that were mild or moderate in intensity.

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 remained stable during open-label experience (1.63 per 100 patient-years) compared to the double-blind experience (2.07 per 100 patient-years). The most frequently reported autoimmune-related disorder during the open-label experience was psoriasis.

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 neutralizing antibodies. Twenty-two of 48 evaluable patients showed significant neutralizing activity. The potential clinical relevance of neutralizing 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.

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

Attachment 1: Product information AusPAR Orencia Abatacept Bristol Myers Squibb Australia Ltd - PM-2016-03491-1-3 Final 4 February 2019 This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>

Table 5: Adverse Drug Reactions (ADRs) Occurring in ³ 1% of Patients in the ORENCIA+MTX in AGREE (IM101023)

Related Adverse Event (Preferred Term)	ORENCIA+MTX	Placebo+MTX
	n=256 %	n=253 %
<i>Infections and Infestations</i>		
bronchitis	3.9	1.2
nasopharyngitis	3.1	2.0
urinary tract infection	2.3	2.8
upper respiratory tract infection	2.3	2.4
oral herpes	2.0	1.2
pharyngitis	2.0	0.4
influenza	1.6	2.8
herpes zoster	1.2	1.2
<i>Gastrointestinal Disorders</i>		
nausea	4.3	4.3
mouth ulceration	1.6	0.4
diarrhoea	1.2	2.4
<i>Nervous System Disorders</i>		
headache	3.5	3.6
dizziness	3.5	2.4
<i>Investigations</i>		
alanine aminotransferase increased	3.1	2.4
aspartate aminotransferase increased	2.0	1.6
weight increased	1.2	0
<i>Respiratory, Thoracic and Mediastinal Disorders</i>		
cough	2.7	1.6
<i>General Disorders and Administration Site Conditions</i>		
fatigue	1.2	1.2
<i>Vascular Disorders</i>		
hypertension	1.2	1.6

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

ADRs reported in less than 1% of patients receiving ORENCIA^o + MTX in the AGREE Trial and not listed in Table 11 are listed below by body system.

Blood and lymphatic system anaemia disorders:

<i>Ear and labyrinth disorders:</i>	vertigo
<i>Eye disorders:</i>	eye irritation, presbyopia
<i>Gastrointestinal disorders:</i>	vomiting, abdominal pain upper, dry mouth, dyspepsia, abdominal pain, gastritis, gastrointestinal haemorrhage, gastrointestinal pain, gingival ulceration, lip dry
<i>General disorders and administration conditions:</i>	malaise, chest pain, asthenia, chest discomfort, axillary pain, chills, feeling hot, infusion-related reaction, infusion site erythema, infusion site pain, sudden death
<i>Hepatobiliary disorders:</i>	hepatic function abnormal
<i>Immune system disorders:</i>	hypersensitivity
<i>Infections and infestations:</i>	gastroenteritis, tooth abscess, pneumonia, respiratory tract infection, sinusitis, tonsillitis, viral upper respiratory tract infection, acariasis, furuncle, genital herpes, tinea pedis, acarodermatitis, bacterial infection, bronchopneumonia, cystitis, ear infection, fungal rash, laryngitis, lung infection pseudomonal, rhinitis, sepsis, soft tissue infection, tinea versicolour, vaginal infection
<i>Injury, poisoning and procedural complications:</i>	contusion
<i>Investigations:</i>	transaminases increased, gamma-glutamyltransferase increased, blood alkaline phosphatase increased, blood pressure increased
<i>Metabolism and nutrition disorders:</i>	diabetes mellitus
<i>Musculoskeletal and connective tissue disorders:</i>	back pain, joint swelling, ligament disorder, musculoskeletal stiffness, pain in extremity, systemic lupus erythematosus
<i>Neoplasms benign, malignant and unspecified (includes cysts and polyps):</i>	lung neoplasm, skin papilloma
<i>Nervous system disorders:</i>	dysgeusia, paraesthesia
<i>Psychiatric disorders:</i>	depression, insomnia, nervousness
<i>Reproductive system and breast disorders:</i>	breast mass, breast pain
<i>Respiratory, thoracic and mediastinal disorders:</i>	nasal congestion, pharyngolaryngeal pain, rhinorrhoea, sinus congestion, dyspnoea exertional, nasal discomfort, nasal dryness
<i>Skin and subcutaneous tissue disorders:</i>	rash, alopecia, urticaria, acne, eczema, nail dystrophy, pruritus, psoriasis, skin lesion
<i>Vascular disorders:</i>	flushing, hyperaemia, hypotension

Clinical experience in Study VII (IM101043)

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.

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, Study 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 enrollment, 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 trial experience in adult RA patients treated with subcutaneous ORENCIA

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

Study SC-I was a randomized, double-blind, double-dummy, non-inferiority study that compared the efficacy and safety of abatacept administered subcutaneously (SC) (with IV loading dose) and intravenously (IV) in 1457 subjects with rheumatoid arthritis, receiving background methotrexate, 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 randomized, 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 rheumatoid arthritis, receiving background methotrexate, and experiencing an inadequate response to MTX (MTX-IR) (see 5.1 Pharmacodynamic Properties - Clinical Trials). 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 subcutaneous or intravenous 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 subcutaneous 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.

Immunogenicity in Adult RA Patients Treated with SC Abatacept

Study SC-I compared the immunogenicity to abatacept following subcutaneous or intravenous administration. The overall immunogenicity frequency to abatacept was 1.1% (8/725) and 2.3% (16/710) for the subcutaneous and intravenous 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 (IM101173) was conducted to determine the effect of monotherapy use of ORENCIA on immunogenicity following subcutaneous administration without an intravenous load in 100 RA patients, who had not previously received abatacept or other CTLA4Ig, who received either subcutaneous ORENCIA+MTX(n=51) or subcutaneous ORENCIA monotherapy (n=49). No patients in either group developed anti-product antibodies after 4 months of treatment. The safety observed in this study was consistent with that observed in the other subcutaneous studies.

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

Study SC-III (IM101167) in the subcutaneous program was conducted to investigate the effect of withdrawal (three months) and restart of ORENCIA subcutaneous treatment on immunogenicity in RA patients treated concomitantly with methotrexate. One hundred sixty-seven patients were enrolled in the first 3-month treatment period and responders (n=120) were randomized to either subcutaneous ORENCIA or placebo for the second 3-month period (withdrawal period). Patients from this period then received open-label ORENCIA treatment in the final 3-month period of the study (period 3). At the end of the withdrawal period, 0/38 patients who continued to receive subcutaneous ORENCIA developed anti-product antibodies compared to 7/73 (9.6%) of patients who had subcutaneous ORENCIA withdrawn during this period. Half of the patients receiving subcutaneous placebo during the withdrawal period received a single intravenous infusion of ORENCIA at the start of Period 3 and half received intravenous placebo prior to reinitiating subcutaneous ORENCIA in Period 3. At the end of Period 3, when all patients again received subcutaneous ORENCIA, the immunogenicity rates were 1/38 (2.6%) in the group receiving subcutaneous 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 subcutaneous therapy for up to 3 months relative to those who remained on subcutaneous therapy, whether therapy was reintroduced with or without an intravenous loading dose. 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 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 (for example, psoriasis, Raynaud's phenomenon, erythema nodosum), 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.

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 (eg, pruritus, throat tightness, dyspnoea) have been received following the use of SC ORENCIA.

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.

Summary of the safety profile in Psoriatic Arthritis (PsA)

ORENCIA has been studied in patients with active psoriatic arthritis 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 $\geq 2\%$ 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 Paediatric and Adolescent 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 4.4 Special Warnings and Precautions for Use and 4.8 Adverse Effects (Undesirable Effects)).

ORENCIA has been studied in 190 paediatric patients; 6 to 17 years of age, with polyarticular juvenile idiopathic arthritis (see 5.1 Pharmacodynamic Properties - Clinical Trial). 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, diarrhoea, cough, pyrexia, and abdominal pain.

A total of 6 serious adverse events (acute lymphocytic leukemia, ovarian cyst, varicella infection, disease flare [2], and joint wear) were reported 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, 6month, 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 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 multiple sclerosis 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 $\geq 5\%$ of pediatric 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 6 below by system organ classification. All adverse events listed below fall into the frequency category of common ($\geq 1\%$ - $<10\%$), as defined above for adult RA.

Table 6: Adverse Events in Placebo-Controlled Trials (regardless of causality) at $\geq 5\%$ for Period B (double-blind phase)

System Organ Classification / Preferred Term	ORENCIA n (%)	Placebo^a n (%)
Number treated	60 (100)	62 (100)
<i>Infections and infestations</i>		
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)
<i>Gastrointestinal disorders</i>		
Abdominal pain	3 (5.0)	1 (1.6)
<i>General disorders and administration site conditions</i>		
Pyrexia	4 (6.7)	5 (8.1)
<i>Nervous system disorders</i>		
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 randomized into one of 2 arms (in Period B), and either continued on ORENCIA or withdrew from ORENCIA to

receive placebo. See 5.1 Pharmacodynamic properties – Mechanism of action – clinical trials - Paediatric and Adolescent (Juvenile Idiopathic Arthritis).

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. Each ADR was a single ADR case yielding an incidence of 1.7%, no ADR with a frequency of less than 1% was reported.

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 titers at baseline had positive titers at Day 113. In Period B, 5.9% of ORENCIA-treated patients and 4.0% of placebo patients that had negative antinuclear antibody titers at baseline had positive titers at Day 169.

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

Immunogenicity

Antibodies directed against the entire abatacept molecule or to the CTLA-4 portion of abatacept were assessed by ELISA assays in 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 randomized 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 titer. The absence of concomitant methotrexate (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 events 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.

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at <http://www.tga.gov.au/reporting-problems>.

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 information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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.

Pharmacology

General

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 TNF α , interferon- γ and interleukin-2 production by T lymphocytes. In a rat collagen-induced arthritis model, abatacept suppresses inflammation, decreases anti-collagen antibody production and reduces antigen specific production of interferon- γ

Pharmacodynamics

Dose finding studies were conducted with abatacept monotherapy (placebo, 0.5 mg/kg, 2 mg/kg, and 10 mg/kg) and in combination with 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 2 mg/kg and 10 mg/kg. In clinical trials with ORENCIA using doses approximating 10 mg/kg, inhibition of T lymphocyte activation, decreases in products of macrophages, fibroblast-like synoviocytes, and B cells, and reductions in acute phase reactants of inflammation were observed. Decreases were seen in: serum levels of soluble interleukin-2 receptor, a marker of T lymphocyte activation; serum interleukin-6, a product of activated macrophages and fibroblast-like synoviocytes; rheumatoid factor, an autoantibody produced by plasma cells; and C-reactive protein, an acute phase reactant of inflammation. In addition, serum levels of matrix metalloproteinase-3, which produces cartilage destruction and tissue remodeling, were decreased. Reductions in serum TNF α were also observed. These changes are consistent with the mechanism of action of this selective costimulation modulator.

Clinical trials

Adult Rheumatoid Arthritis in Patients treated with intravenous ORENCIA

Clinical trials

The efficacy and safety of ORENCIA for intravenous administration were assessed in six randomized, double-blind, placebo-controlled studies in patients³ 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), 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 randomization. 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 randomization; other DMARDs were permitted. Study V primarily assessed safety in patients with active RA requiring additional intervention in spite of current therapy with DMARDs; all DMARDs used at enrollment were continued. In Study VI, the efficacy and safety of ORENCIA were assessed in MTX-naive patients with early, erosive RA (\leq 2 years disease duration). In Study VI, patients previously naive to MTX were randomized to receive ORENCIA+MTX or MTX+placebo.

In Study VI, the efficacy and safety of abatacept were assessed in methotrexate-naive, Rheumatoid Factor (RF) and/or anti-Cyclic Citrullinated Peptide 2 (Anti-CCP2)-positive patients with early, erosive rheumatoid arthritis (\leq 2 years disease duration) who were randomized to receive abatacept plus methotrexate or methotrexate plus placebo. For all patients randomized and treated, the median age was 51 years, the median disease duration was 3 months and the median tender and swollen joint counts were 28 and 20, respectively. Patients were randomized to receive abatacept (10 mg/kg, weight-tiered dose)+MTX or MTX+placebo for the first 12 months of treatment. In both groups, the

MTX dose was titrated to at least 15 mg per week not to exceed 20 mg per week. The co-primary endpoints of this study were the proportion of subjects in abatacept+MTX group versus MTX+placebo who achieved DAS28-CRP remission and to compare inhibition of joint damage progression measured by the Genant-modified Sharp total score at 12 months of treatment.

Study I patients were randomized 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 randomized to receive ORENCIA 2 or 10 mg/kg or placebo for 12 months. For Studies I and II, only results in the 10 mg/kg group are discussed below. Studies III, IV, V and VI patients were randomized 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 7. 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, IV and VI, 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 7: 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 ^c SC +MTX n=693	Abatacept ^c 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 7). 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 8.

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 8: 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

^aBased on non-parametric analysis.

In the open-label extension of Study III, 75% (n=324) of patients initially randomized 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 \leq 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 methotrexate and switched to combination with abatacept had no progression.

Table 9: Mean Radiographic Changes Over 12 and 24 Months in Study VI

Parameter	Month 12		P-value ^a	Month 24	
	ORENCIA+ MTX n=242	Placebo +MTX n=242		ORENCIA+ MTX n=213	Placebo +MTX n=192
Total Sharp score					
Baseline (Mean)	7.50	6.67		7.73	7.24
Change from Baseline (Mean)	0.63	1.06	0.040	0.84	1.75
Erosion score					
Baseline (Mean)	5.48	4.81		5.91	5.49
Change from Baseline (Mean)	0.50	0.89	0.033	0.59	1.40
JSN score					
Baseline (Mean)	2.03	1.86		1.83	1.75
Change from Baseline (Mean)	0.13	0.17	0.353	0.25	0.34

^a Based on non-parametric analysis.

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 ³0.3 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,

Attachment 1: Product information AusPAR Orencia Abatacept Bristol Myers Squibb Australia Ltd - PM-2016-03491-1-3 Final 4 February 2019 This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>

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 10. 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 10: 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 ³0.3 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 Study VI, a greater reduction in the fatigue score was observed at 6 and 12 months in ORENCIA+MTX-treated patients than in MTX+placebo-

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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 rheumatoid arthritis

Study VII: abatacept or infliximab versus placebo

A randomized, double-blind study was conducted to assess the safety and efficacy of abatacept or infliximab versus placebo in patients with an inadequate response to methotrexate (Study VII, Study 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 randomized 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 11, as are the percentages of patients achieving DAS28-defined low disease activity and remission. Greater improvement ($p < 0.001$) in DAS28 was observed with abatacept and with infliximab compared to placebo at 6 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 randomized 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 11: 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.

^aPlacebo 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, Study 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 enrollment, 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.

Adult Rheumatoid Arthritis in Patients treated with subcutaneous ORENCIA

Clinical trials

Study SC-I (IM101174) was a randomized, 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 rheumatoid arthritis (RA), receiving background methotrexate (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 2, the study demonstrated non-inferiority of ORENCIA administered subcutaneously vs. intravenously with respect to ACR 20 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 randomized with stratification by body weight (<60 kg, 60 to 100 kg, >100 kg) to receive ORENCIA 125 mg subcutaneous 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 randomization.

Study SC-IV (IM101235) 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 subcutaneous ORENCIA relative to subcutaneous adalimumab in subjects with moderate to severely active RA and experiencing inadequate response to MTX.

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

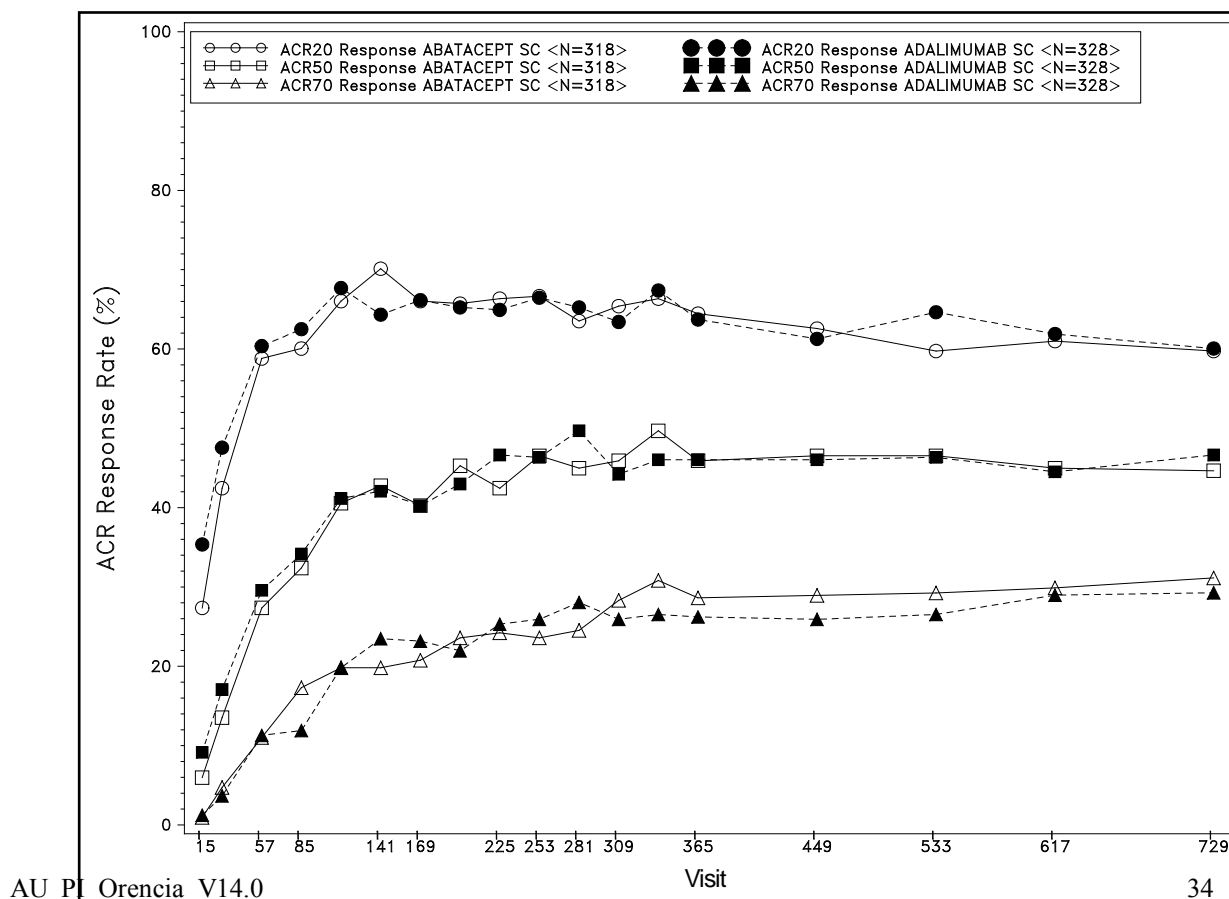
Clinical response

ACR response

In Study SC-I, ORENCIA administered subcutaneously (SC) was non-inferior relative to intravenous (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 intravenous and subcutaneous treatment groups in subgroups based on weight categories (less than 60 kg, 60 to 100 kg, and more than 100 kg; data not shown). 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 2.

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 Randomized 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 13. The proportion of subjects without radiographic progression in Total Score defined as a change from baseline \leq 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 13: Mean Radiographic Change from Baseline (SD)^a Over 12 and 24 Months in Study SC-IV

Parameter	ORENCIA 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)

^aSD = standard deviation

^bEstimated 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 subcutaneous and intravenous administration.

Clinical trial experience in adult Psoriatic Arthritis (PsA) patients treated with ORENCIA

The efficacy and safety of ORENCIA were assessed in two randomized, 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 (IV) 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 randomized 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 methotrexate, low dose corticosteroids (equivalent to ≤ 10 mg of prednisone) and/or NSAIDs during the trial.

In Study PsA-II, 424 patients were randomized 1:1 to receive in a double-blind manner weekly doses of subcutaneous (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 methotrexate, 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 14 below.

Table 14: 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-naïve 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-naïve 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 ³ 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 ³ 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.

Paediatric and Adolescent (Juvenile Idiopathic Arthritis)

The safety and efficacy of ORENCIA were assessed in a three-part study (IM101033, AWAKEN) including an open-label extension in children with polyarticular juvenile idiopathic arthritis (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/m² 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 utilizing the ACR Paediatric 30 definition of improvement, defined as ≥30% improvement in at least 3 of the 6 JIA core set variables and ≥30% worsening in not more than 1 of the 6 JIA core set variables. Patients demonstrating an ACR Pedi 30 response at the end of Period A were randomized into the double-blind phase (Period B) and received either ORENCIA or placebo for 6 months or until disease flare. Disease flare was defined as a ≥30% worsening in at least 3 of the 6 JIA core set variables with ≥30% improvement in not more than 1 of the 6 JIA core set variables; ≥2 cm of worsening of the Physician or Parent Global Assessment was necessary if 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 randomized withdrawal phase (Period B), ORENCIA-treated patients experienced significantly fewer disease flares compared to placebo-treated patients (20% vs. 53%); 95% CI of the difference (15%, 52%). The risk of disease flare among patients continuing on ORENCIA was less than one third 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.

There is no clinical trial data for the use of ORENCIA subcutaneous 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 – Intravenous Infusion

Absorption

Abatacept is administered intravenously.

Distribution

The pharmacokinetics of abatacept were studied in healthy adult subjects after a single 10 mg/kg intravenous infusion and in RA patients after multiple 10 mg/kg intravenous infusions (see Table 15).

Table 15: 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)

Table 15: 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
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 (V _{ss}) [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 intravenous infusions, the pharmacokinetics of abatacept showed proportional increases of C_{max} and AUC over the dose range of 2 mg/kg to 10 mg/kg. At 10 mg/kg, serum concentration appeared to reach a steady-state by Day 60 with a mean (range) trough concentration of 24 (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 - Subcutaneous Administration

Absorption

Abatacept is administered subcutaneously.

Distribution

Abatacept exhibited linear pharmacokinetics following subcutaneous 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 subcutaneous administration relative to intravenous 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 subcutaneous 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 psoriatic arthritis

In PsA-I, patients were randomized 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 metabolized 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 juvenile idiopathic arthritis (JIA) aged 6 to 17 years following administration of abatacept 10 mg/kg revealed that the estimated clearance of abatacept, when normalized 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 normalized 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 methotrexate, 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

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

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the ARTG. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

ORENCIA lyophilized powder must be refrigerated at 2°C to 8°C. For storage of the fully diluted ORENCIA solution, see Section 4.2 Dose and method of administration.

ORENCIA injection 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, prefilled syringes, and autoinjectors from light by storing in the original package until time of use.

6.5 NATURE AND CONTENTS OF CONTAINER

For Intravenous 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. All components of the syringe are latex-free. The product is available in the strength of 250 mg of abatacept in a 15-mL vial.

For Subcutaneous Injection

ORENCIA (abatacept) injection 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, a 1 mL single-dose disposable prefilled glass syringe with a passive needle guard and flange extenders (pfs-ssi-fe), 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 4 1 mL prefilled syringes or autoinjectors.

Not all presentations may be available.

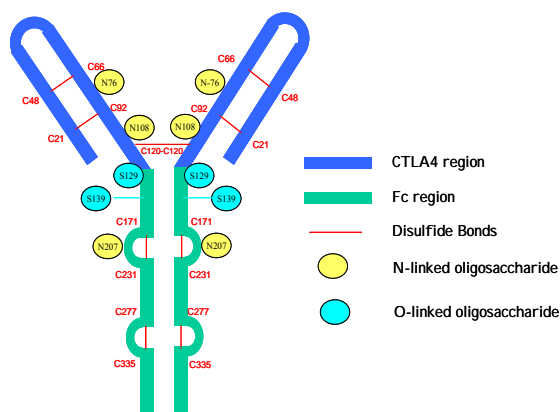
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Abatacept structure:



CAS number

332348-12-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription Only Medicine.

Attachment 1: Product information AusPAR Orencia Abatacept Bristol Myers Squibb Australia Ltd - PM-2016-03491-1-3 Final 4 February 2019 This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>

8 SPONSOR

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9 DATE OF FIRST APPROVAL (ARTG ENTRY)

27 September 2007

10 DATE OF REVISION OF THE TEXT

12 January 2018

SUMMARY TABLE OF CHANGES

Section Changed		Summary of new information
All		TGA Approved ORENCIA PI V13.0 (12 April 2017) converted to new TGA format
4.1		New indication added for active psoriatic arthritis in adults
4.2, 4.4, 4.8, 5.1, 5.2		New information related to dosing, precautions, adverse effects, clinical trials and pharmacokinetics for the new indication added

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