

Data Sheet

Name of Medicine

ORENCIA[®]
abatacept

Presentation

Orencia[®] is supplied as an individually packaged, single-use vial with a silicone-free disposable syringe. It 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, colorless to pale yellow, with a pH range of 7.2 to 7.8. Each single-use vial provides 250mg abatacept, 500mg maltose, 17.2mg sodium phosphate monobasic and 14.6mg of sodium chloride. The product is available in the strength of 250 mg of abatacept in a 15-mL vial.

Uses

Actions

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

Abatacept modulates a key costimulatory signal required for full activation of T lymphocytes expressing CD28. T lymphocytes are found in the synovium of patients with RA. Activated T lymphocytes contribute to the pathogenesis of RA and other autoimmune diseases. Full activation of T lymphocytes requires two signals provided by antigen presenting cells: recognition of a specific antigen by a T cell receptor (signal 1) and a second, costimulatory signal. A major costimulatory pathway involves the binding of CD80 and CD86 molecules on the surface of antigen presenting cells to the CD28 receptor on T lymphocytes (signal 2). Abatacept binds specifically to CD80 and CD86 inhibiting this costimulatory pathway. Studies indicate that abatacept affects both memory and naïve T lymphocyte responses.

Studies *in vitro* and in animal models demonstrate that abatacept attenuates T lymphocyte dependent antibody responses and inflammation. *In vitro*, abatacept attenuates T lymphocyte activation as measured by decreased proliferation and cytokine production in human lymphocytes. Abatacept decreases antigen specific 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 .

Dose finding studies were conducted with abatacept monotherapy (placebo, 0.5 mg/kg, 2 mg/kg, and 10 mg/kg) and in combination with MTX (placebo, 2 mg/kg, and 10 mg/kg). In both studies, the American College of Rheumatology (ACR) 20 response rate increased with increasing doses at 2mg/kg and 10 mg/kg. In clinical trials with **Orencia**[®] using doses approximating 10mg/kg, inhibition of T lymphocyte activation, decreases in products of macrophages, fibroblast-like

synoviocytes, and B cells, and reductions in acute phase reactants of inflammation were observed. Decreases were seen in: serum levels of soluble interleukin-2 receptor, a marker of T lymphocyte activation; serum interleukin-6, a product of activated macrophages and fibroblast-like synoviocytes; rheumatoid factor, an autoantibody produced by plasma cells; and C-reactive protein, an acute phase reactant of inflammation. In addition, serum levels of matrix metalloproteinase-3, which produces cartilage destruction and tissue remodeling, were decreased. Reductions in serum TNF α were also observed. These changes are consistent with the mechanism of action of this selective costimulation modulator.

CLINICAL TRIAL EFFICACY INFORMATION

Adult Rheumatoid Arthritis

Clinical trials

The efficacy and safety of **Orencia**[®] were assessed in six randomized, double-blind, placebo-controlled studies in patients \geq age 18 with active RA diagnosed according to American College of Rheumatology (ACR) criteria. The trials are designated as follows: Study I (IM103002), Study II (IM101100), Study III (IM101102, AIM), Study IV (IM101029, ATTAIN), and Study V (IM101031, ASSURE) and Study VI (IM101023, AGREE). Studies I, II, III, IV, and VI required patients to have at least 12 tender and 10 swollen joints at 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 enrolment were continued. In Study VI, the efficacy and safety of **Orencia**[®] were assessed in MTX-naïve patients with early (\leq 2 years disease duration), severe active (tender joint count of at least 12, swollen joint count of at least 10, and a CRP of \geq 0.45 mg/dL) erosive (erosion of the hands, wrists, or feet on radiograph) RA. In Study VI, patients previously naïve to MTX were randomized to receive **Orencia**[®] plus MTX or MTX plus placebo.

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 10mg/kg group are discussed below. Study 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 1. Month 6 and 12 ACR response rates in Study II for the

10 mg/kg group were similar to the **Orencia**[®] group in Study III. ACR response rates at 3 months in Study I were supportive of these findings.

In Studies III and IV, improvement in the ACR 20 response rate versus placebo was observed after administration of the first dose, as measured at day 15, and was maintained through the double-blind study period. In Study VI, improvement in the ACR 20 response rate in **Orencia**[®]+MTX-treated patients versus MTX+placebo-treated patients was observed at 29 days, and was maintained through the double-blind study period. The ACR 50 response with **Orencia**[®] was significantly greater than placebo at months 2 and 3, respectively, for Studies III and IV, with continued improvement in the ACR50 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, 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 (Study 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 1: Clinical Responses in Controlled Trials

	Percent of Patients					
	MTX-Naive		Inadequate Response to MTX		Inadequate Response to TNF Blocking Agent	
	Study VI		Study III		Study IV	
Response Rate	Abatacept ^a + MTX n=256	Placebo +MTX n=253	Abatacept ^a +MTX n=424	Placebo +MTX n=214	Abatacept ^a + DMARDs ^b n=256	Placebo + DMARDs ^b n= 133
ACR 20						
Month 3	64%*	53%	62%***	37%	46%***	18%
Month 6	75%**	62%	68%***	40%	50%***	20%
Month 12	76%***	62%	73%***	40%	NA	NA
ACR 50						
Month 3	40%***	23%	32%***	8%	18%**	6%
Month 6	53%***	38%	40%***	17%	20%***	4%
Month 12	57%***	42%	48%***	18%	NA	NA
ACR 70						
Month 3	19%**	10%	13%***	3%	6%*	1%
Month 6	32%**	20%	20%***	7%	10%**	2%
Month 12	43%***	27%	29%***	6%	NA	NA
Major Clinical Response^c	27%***	12%	14%***	2%	NA	NA
DAS28-CRP Remission^d						
Month 12	41%***	23%	NA	NA	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).

^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

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 II, 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**[®] plus MTX had a higher DAS28-CRP remission rate at 12 months than those treated with MTX plus placebo (Table 1). Of patients treated with **Orencia**[®] plus 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 placebo/MTX after 12 months of treatment as shown in Table 2.

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 2: Mean Radiographic Changes Over 12 Months in Study III

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

^a Based on non-parametric analysis.

In the open-label extension of Study III, 75% (n = 324) of patients initially 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**[®] plus MTX compared to those treated with MTX plus placebo. At 12 months 61% (148/242) of the patients treated with abatacept plus methotrexate and 53% (128/242) of the patients treated with methotrexate plus placebo had no progression (change from baseline in ~~TSS~~ **TSS**). Among the patients who entered the open-label 12 month period, the progression of structural damage was lower in those receiving continuous abatacept plus methotrexate treatment (for 24 months) compared to patients who initially received methotrexate plus placebo (for 12 months) and were switched to abatacept plus methotrexate for the next 12 months. Of these patients, 57% (121/213) who received continuous abatacept plus methotrexate treatment and 44% (84/192) of patients who initially received methotrexate and switched to combination with abatacept had no progression.

The effect of **Orencia**[®] on structural damage was not studied in RA patients with an inadequate response to TNF blocking agents.

Physical function response

Improvement in physical function was measured by the Health Assessment Questionnaire Disability Index (HAQ-DI) in Studies III, IV, and V, and a modified HAQ-DI in Study II. In Studies II-V, **Orencia**[®] demonstrated significantly greater improvement from baseline than placebo in the HAQ-DI and a significantly greater proportion of patients treated with **Orencia**[®] compared to placebo showed a clinically meaningful improvement (reduction in HAQ-DI of ≥ 0.3 units from baseline). In Study VI, significantly greater improvement from baseline in the HAQ-DI was observed in **Orencia**[®]+MTX-treated patients compared with MTX+placebo-treated patients, and significantly more patients in the **Orencia**[®]+MTX group compared with the MTX+placebo group achieved a clinically meaningful improvement at 12 months. In Study III, among HAQ responders at month 12, 88% retained the response at month 18, and 85% retained the response at month 24. The results from Studies II-IV are shown in Table 3. 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, and 2 years, respectively.

Table 3: Mean Improvement from Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI)

	Inadequate Response to Methotrexate (MTX)				Inadequate Response to TNF Blocking Agent	
	Study II		Study III		Study IV	
HAQ Disability Index	ORENCIA [®] ^a +MTX	Placebo +MTX	ORENCIA [®] ^b +MTX	Placebo +MTX	ORENCIA [®] ^b +DMARDs ^c	Placebo +DMARDs ^c
Baseline (Mean)	0.98 ^d (n=115)	0.97 ^d (n=119)	1.69 ^e (n=422)	1.69 ^e (n=212)	1.83 ^e (n=249)	1.82 ^e (n=130)
Mean Improvement from Baseline						
Month 6	0.40 ^{d,***} (n=113)	0.19 ^d (n=118)	0.59 ^{e,***} (n=420)	0.40 ^e (n=211)	0.45 ^{e,***} (n=249)	0.11 ^e (n=130)
Month 12	0.40 ^{d,***} (n=115)	0.15 ^d (n=119)	0.66 ^{e,***} (n=422)	0.37 ^e (n=212)	NA	NA
Proportion of patients with a clinically meaningful improvement ^f						
Month 6	47% ^{d,**}	28% ^d	61% ^{e,***}	45% ^e	47% ^{e,***}	23% ^e
Month 12	38% ^{d,**}	20% ^d	64% ^{e,***}	39% ^e	NA	NA

** p <0.01, ORENCIA[®] vs. placebo.

*** p <0.001, ORENCIA[®] vs. placebo.

^a 10 mg/kg.

^b Fixed dose approximating 10 mg/kg

^c Concurrent DMARDs included one or more of the following: MTX, azathioprine, chloroquine/hydroxychloroquine, gold, leflunomide, sulfasalazine, and anakinra.

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

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

^f Reduction in HAQ-DI of ≥0.3 units from baseline.

Health-related outcomes and quality of life

Health-related quality of life was assessed by the SF-36 questionnaire at 6 months in Studies II, III, and IV and at 12 months in Studies II and III. In these studies, clinically and statistically significant improvement was observed in the **Orencia**[®] group as compared with the placebo group in all 8 domains of the SF-36 (4 physical domains: physical function, role physical, bodily pain, general health; and 4 mental domains: vitality, social function, role emotional, mental health), as well as the Physical Component Summary (PCS) and the Mental Component Summary (MCS). In Study VI, improvement was observed at 12 months in the **Orencia**[®]+MTX group as compared with the MTX+placebo group in both PCS and MCS and was maintained through 24 months.

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

Additional clinical trials in adult 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 4, 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 six months in the placebo-controlled portion of the trial; the results between the abatacept and infliximab groups were similar. Further improvement was observed at 12 months with abatacept. The ACR responses in Study VII were consistent with the DAS28 score.

The open label period of Study VII provided an assessment of the ability of abatacept to maintain efficacy for subjects originally 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 4: Disease Activity Score 28 (DAS28 ESR) Results in Study VII

	Abatacept +MTX n = 150	Infliximab +MTX n = 156	Placebo +MTX n = 102
DAS28 Response			
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 six 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 nonbiologic 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.

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 which 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 Paediatric30 definition of improvement, defined as $\geq 30\%$ improvement in at least 3 of the 6 JIA core set variables and $\geq 30\%$ 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 $\geq 30\%$ worsening in at least 3 of the 6 JIA core set variables with $\geq 30\%$ 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, paediatricACR 30/50/70 responses were 65%, 50%, and 28%, respectively. PaediatricACR 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 paediatricACR 30/50/70 responders has remained consistent for 31 months.

The period C data from the JIA study indicates that efficacy measured by ACR 30, 50, and 70 response rate can occur later in subjects that were initially non-responders following 4 months of abatacept therapy. These data indicates that longer treatment duration may be necessary in some patients before the benefits of abatacept are observed. In both the biologic experienced and the non-biologic experienced non-responders subjects, an incremental benefit is observed following longer therapy with greater response being observed between Days 253 to Days 337 in Period C. Therefore an additional 6 to 9 months (total of 10 to 13 months) of abatacept treatment may be required to observe a benefit in those patients who were not initially responders to 4 months of therapy.

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

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

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.

Pharmacokinetics

Healthy adults and adult RA

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 5).

Table 5: Pharmacokinetic Parameters (Mean, Range) in Healthy Subjects and RA Patients After 10 mg/kg Intravenous Infusion(s)

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

Metabolism and elimination

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

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 and anti-rheumatic drugs (DMARDs).

Orencia[®] may be used concomitantly with methotrexate (MTX).

Orencia[®] should not be administered concurrently with other biological DMARDs (eg, TNF inhibitors, rituximab, or anakinra).

CONTRAINDICATIONS

Orencia[®] should not be administered to patients with known hypersensitivity to **Orencia**[®] or any of its components (see **PRESENTATION**). **Orencia**[®] should not be administered to patients with severe infections such as sepsis, abscesses, tuberculosis, and opportunistic infections.

Dosage and Administration

For adult patients with RA, **Orencia**[®] should be administered as a 30-minute intravenous infusion utilizing the weight range-based dosing specified in Table 6. Following the initial administration, **Orencia**[®] should be given at 2 and 4 weeks after the first infusion, then every 4 weeks thereafter. Methotrexate, other non-biologic DMARDs, corticosteroids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics may be used during treatment with **Orencia**[®].

Table 6: Dose of ORENCIA^{®a}

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 Paediatric and adolescent).

Renal impairment, hepatic impairment

Orencia[®] has not been studied in these patient populations. No dose recommendations can be made.

Paediatric and adolescent

Juvenile Idiopathic Arthritis. The recommended dose of ORENCIA[®] for patients 6 to 17 years of age with juvenile idiopathic arthritis who weigh less than 75 kg is 10 mg/kg calculated based on the patient's body weight at each administration. Paediatric patients weighing 75 kg or more should be administered ORENCIA[®] following the adult dosing regimen, not to exceed a maximum dose of 1000 mg. ORENCIA[®] should be administered as a 30-minute 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.

Use in the elderly

No dose adjustment is required (see PRECAUTIONS).

Concomitant therapy

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

PREPARATION AND ADMINISTRATION INSTRUCTIONS

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 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 colorless to pale yellow. Do not use if opaque particles, discoloration, 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 discoloration. Discard the solution if any particulate matter or discoloration 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.

For information on **Orencia**[®], contact Bristol-Myers Squibb, Australia 1800-067567

WARNINGS AND PRECAUTIONS

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 **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**[®] 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. Hypersensitivity

was reported uncommonly. Other events potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, that occurred within 24 hours of **Orencia**[®] infusion, were uncommon.

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**[®]. In clinical studies with **Orencia**[®], patients who screened positive for hepatitis were excluded from study.

Malignancies

In the placebo-controlled clinical trials in adult RA, the frequencies of malignancies in abatacept- and placebo-treated patients were 1.4% and 1.1%, respectively (see ADVERSE REACTIONS). 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 CARCINOGENICITY). The potential role of **Orencia**[®] in the development of malignancies, including lymphoma, in humans is unknown.

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.

Interactions with other medicines.

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 **PHARMACOKINETICS**)

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.

Other Interactions

Blood Glucose Testing.

Parenteral drug products containing maltose can interfere with the readings of blood glucose monitors that use test strips with glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ). The GDH-PQQ based glucose monitoring systems may react with the maltose present in **Orencia**[®], resulting in falsely elevated blood glucose readings on the day of infusion. When receiving **Orencia**[®], patients that require blood glucose monitoring should be advised to consider methods that do not react with maltose, such as those based on glucose dehydrogenase nicotinic adenine dinucleotide (GDH-NAD), glucose oxidase, or glucose hexokinase test methods.

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.

Effects in non-human primates

In a one-year toxicity study in 30 cynomolgus monkeys at weekly doses of 10-50 mg/kg, abatacept (2-9-fold the human exposure based on the AUC), drug related effects consisted of minimal transient decreases in serum immunoglobulin G and minimal to severe lymphoid depletion of germinal centres in the spleen and/or lymph nodes, which were consistent with the pharmacological

activities of the drug. No lymphomas or pre-neoplastic morphological changes were observed, despite the presence of a virus (lymphocryptovirus) known to cause these lesions in immunosuppressed monkeys.

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)

Abatacept may affect the immune system in the fetus. 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. There are no adequate and well-controlled studies in pregnant women. The use of **Orencia**[®] during pregnancy is not recommended.

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.

Pediatric 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 and anti-rheumatic drugs (DMARDs). **ORENCIA**[®] may be used 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 has not been established.

The long-term effects of **Orencia**[®] therapy on skeletal, behavioural, cognitive, sexual, and immune maturation and development in children are unknown.

Non-clinical studies relevant for use in the paediatric population

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

Use in the elderly

A total of 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.

Patients on controlled sodium diet

This medicinal product contains 1.5mmol (or 34.5mg) 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 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 dyspnea. Use of **Orencia**[®] in patients with rheumatoid arthritis and COPD should be undertaken with caution and such patients should be monitored for worsening of their respiratory status.

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.

Adverse Effects

Adult

General

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 7.

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 8).

Table 7 : 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 8: 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%
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 ≥10%; common ≥1% <10%; uncommon ≥0.1% <1%; rare ≥0.01% <0.1%).

Infections and infestations

- Common: Lower respiratory tract infection (including, bronchitis), urinary tract infection, herpes simplex, upper respiratory tract infection (including tracheitis, nasopharyngitis), rhinitis
- Uncommon: Tooth infection, infected skin ulcer, onchomycosis

Neoplasms benign and malignant (including cysts and polyps)

- Uncommon: Basal cell carcinoma

Blood and the lymphatic system disorders

Uncommon: Thrombocytopenia, leukopenia

Psychiatric disorders

Uncommon: Depression, anxiety

Nervous system disorders

Very Common: Headache

Common: Dizziness

Uncommon: Paraesthesia

Eye disorders

Uncommon: Conjunctivitis, visual acuity reduced

Ear and labyrinth disorders

Uncommon: Vertigo

Cardiac disorders

Uncommon: Tachycardia, bradycardia, palpitations

Vascular disorders

Common: Hypertension, flushing

Uncommon: Hypotension, hot flush

Respiratory, thoracic and mediastinal disorders

Common: Cough

Gastrointestinal disorders

Common: Abdominal pain, diarrhoea, nausea, dyspepsia

Uncommon: Gastritis, mouth ulceration, aphthous stomatitis

Skin and subcutaneous tissue disorders

Common: Rash (including dermatitis)

Uncommon: Increased tendency to bruise, alopecia, dry skin

Musculoskeletal, connective tissue and bone disorders

Uncommon: Arthralgia, pain in extremity

Reproductive system and breast disorders

Uncommon: Amenorrhea

General disorders and administration site conditions

Common: Fatigue, asthenia

Uncommon: Influenza like illness

Investigations

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.

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 **WARNINGS** and **PRECAUTIONS**).

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 4149 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 1.43 per 100 patient-years, and the annualised incidence rate remained stable. The incidence rates per 100 patient-years were 0.72 for non-melanomatous skin cancer, 0.59 for solid malignancies and 0.13 for hematologic malignancies. The most frequently reported solid organ cancer was lung cancer (0.17 per 100 patient-years), and the most common hematologic malignancy was lymphoma (0.06 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 9.

Table 9: 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

In the clinical studies with **Orencia**[®], pre-medication to prevent hypersensitivity was not required. Acute infusion-related events (reported within 1 hour of the start of the infusion) in Studies III, IV, and V were more common in the **Orencia**[®]-treated patients than the placebo patients (9.8% for **Orencia**[®], 6.7% for placebo). The most frequently reported events (>1.0%) were dizziness (2.1% for **Orencia**[®], 1.3% for placebo), headache (1.8% for **Orencia**[®], 1.2% for placebo), and hypertension (1.2% for **Orencia**[®], 0.4% for placebo).

Acute infusion-related events that were reported in >0.1% and ≤1% of patients treated with **Orencia**[®] included cardiopulmonary symptoms such as hypotension, increased blood pressure, decreased blood pressure, and dyspnea; other symptoms included nausea, flushing, urticaria, cough, hypersensitivity, pruritus, rash, and wheezing. Most of these reactions were mild to moderate. A small proportion of patients in both the **Orencia**[®] and placebo groups discontinued due to an acute infusion-related event (0.4% for **Orencia**[®], 0.2% for placebo).

The occurrence of anaphylaxis remained rare between the double blind and long-term open-label experience. Hypersensitivity was reported uncommonly. Other events potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, each occurred uncommonly and generally occurred within 24 hours of **Orencia**[®] infusion.

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 dyspnea. 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%]).

Autoantibodies

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

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 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**[®] plus MTX was similar to that in patients receiving MTX alone.

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.

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**[®]. Based on the postmarketing experience with **Orencia**[®] in adult rheumatoid arthritis (RA) patients, the adverse event profile of **Orencia**[®] does not differ from that listed/discussed above in adults.

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.

Paediatric and Adolescent

In general, the adverse events in paediatric patients were similar in frequency and type to those seen in adult patients (see PRECAUTIONS AND ADVERSE EFFECTS).

Orencia[®] has been studied in 190 paediatric patients, 6 to 17 years of age, with polyarticular juvenile idiopathic arthritis (see CLINICAL TRIAL EFFICACY INFORMATION). 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, diarrhea, cough, pyrexia, and abdominal pain.

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

For the 122 patients who responded in the lead-in period and entered the placebo-controlled, 6-month, withdrawal phase, there were no serious adverse events in 60 **Orencia**[®]-treated patients and 3 serious adverse events in 2 of the 62 placebo-treated patients (hematoma 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 9 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 9: Adverse Events in Placebo-Controlled Trials (regardless of causality) at ≥ 5% for Period B(double-blind phase)		
System Organ Classification / Preferred Term	ORENCIA[®] n (%)	Placebo^a n (%)
Number treated	60 (100)	62 (100)
<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 CLINICAL TRIAL EFFICACY INFORMATION: Paediatric and Adolescent (Juvenile Idiopathic Arthritis).

Clinical Trial Adverse Drug Reactions (< 5%)

ADR's reported in less than 5% for Period B (double-blind) for patients receiving **Orencia[®]** in the paediatric clinical trials are listed below by body system.

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

Gastrointestinal disorders: Abdominal pain, nausea, aphthous stomatitis

Skin and subcutaneous tissue disorders: Pityriasis, skin lesion

Nervous system disorders: headache

Renal and urinary disorders: Leukocyturia

Vascular disorders: Hypotension

Infections

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

During the double-blind phase, adverse events of infections were reported in the abatacept and placebo groups [45% and 44%]; influenza 5 [8.3%] vs 4 [6.5%], bacteriuria 4 [6.7%] vs 0 [0%],

nasopharyngitis 4 [6.7%] vs 3 [4.8%], and upper respiratory tract infections 4 [6.7%] vs 5 [8.1%], were the most frequently reported events.

Infusion-related Reactions

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

Autoantibodies

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

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

Immunogenicity

Antibodies directed against the entire abatacept molecule or to the CTLA-4 portion of abatacept were assessed by ELISA assays in 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 reactions or infusional reactions, or with changes in efficacy or serum abatacept concentrations. Of the 54 patients withdrawn from **Orencia**[®] during the double-blind period for up to 6 months, none had an infusion reaction upon re-initiation of **Orencia**[®].

Malignancies

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

Overdose

Orencia[®] is administered as an intravenous infusion under medically controlled conditions. Doses up to 50 mg/kg have been administered 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.

In the event of an overdose or poisoning contact the New Zealand Poisons Information Centre on 03 474 7000

Pharmaceutical Precautions

Shelf Life

3 years

Storage Conditions:

Orencia[®] lyophilized powder must be refrigerated at 2°C to 8°C. For storage of the fully diluted **Orencia**[®] solution, (see **PREPARATION AND ADMINISTRATION**)

Do not use beyond the expiration date.

Protect the vials from light by storing in the original package until time of use.

Medicine Classification

Prescription Medicine

Package Quantities

Infusion 250mg 1's

Further Information

Name and Address:

Bristol-Myers Squibb (NZ) Limited.
Auckland
New Zealand

Date of Preparation: March 2012

NZ_DS_Orencia_FC_V4.0_March 2012