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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

BLA 125118/000

Approved Labeling

ORENCIA[®] (abatacept)

Rx only

DESCRIPTION

ORENCIA[®] (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 (IgG1). Abatacept is produced by recombinant DNA technology in a mammalian cell expression system. The apparent molecular weight of abatacept is 92 kilodaltons.

ORENCIA is supplied as a sterile, white, preservative-free, lyophilized powder for parenteral administration. Following reconstitution with 10 mL of Sterile Water for Injection, USP, the solution of ORENCIA is clear, colorless to pale yellow, with a pH range of 7.0 to 8.0. Each single-use vial of ORENCIA provides 250 mg abatacept, 500 mg maltose, 17.2 mg monobasic sodium phosphate, and 14.6 mg sodium chloride for administration.

CLINICAL PHARMACOLOGY

Mechanism of Action

Abatacept, a selective costimulation modulator, inhibits T cell (T lymphocyte) activation by binding to CD80 and CD86, thereby blocking interaction with CD28. This interaction provides a costimulatory signal necessary for full activation of T lymphocytes, implicated in the pathogenesis of rheumatoid arthritis (RA). Activated T lymphocytes are found in the synovium of patients with RA.

In vitro, abatacept decreases T cell proliferation and inhibits the production of the cytokines tumor necrosis factor alpha (TNF α), interferon- γ , and interleukin-2. In a rat collagen-induced arthritis model, abatacept suppresses inflammation, decreases anti-collagen antibody production, and reduces antigen specific production of interferon- γ . The relationship of these biological response markers to the mechanisms by which ORENCIA exerts its effects in RA is unknown.

Pharmacodynamics

In clinical trials with ORENCIA at doses approximating 10 mg/kg, decreases were observed in serum levels of soluble interleukin-2 receptor (sIL-2r), interleukin-6 (IL-6), rheumatoid factor (RF), C-reactive protein (CRP), matrix metalloproteinase-3 (MMP3), and tumor necrosis factor alpha (TNF α). The relationship of these biological response markers to the mechanisms by which ORENCIA exerts its effects in RA is unknown.

Pharmacokinetics

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 1).

Table 1: 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)

^aMultiple 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 methotrexate (MTX), nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and TNF blocking agents did not influence abatacept clearance.

The pharmacokinetics of abatacept have not been studied in children and adolescents. No formal studies were conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of abatacept.

CLINICAL STUDIES

The efficacy and safety of ORENCIA were assessed in five randomized, double-blind, placebo-controlled studies in patients \geq age 18 with active RA diagnosed according to American College of Rheumatology (ACR) criteria. Studies I, II, III, and IV 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 evaluated ORENCIA as monotherapy in 122 patients with active RA who had failed at least one non-biologic, disease-modifying, anti-rheumatic drug (DMARD) or etanercept. 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. Patients in Study V were not excluded for comorbid medical conditions.

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. Study III, IV, and V patients were randomized to receive a dose of ORENCIA based on weight range or placebo for 12 months (Studies III and V) 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

The percent of ORENCIA-treated patients achieving ACR 20, 50, and 70 responses and major clinical response in Studies I, III, and IV are shown in Table 2. ORENCIA-treated patients had higher ACR 20, 50, and 70 response rates at 6 months compared to placebo-

treated patients. Month 6 ACR response rates in Study II for the 10 mg/kg group were similar to the ORENCIA group in Study III.

In Studies III and IV, improvement in the ACR 20 response rate versus placebo was observed within 15 days in some patients. In Studies II and III, ACR response rates were maintained to 12 months in ORENCIA-treated patients. ACR responses were maintained up to three years in the open-label extension of Study II.

Table 2: ACR Responses in Placebo-Controlled Trials

	Percent of Patients					
	Inadequate Response to DMARDs		Inadequate Response to MTX		Inadequate Response to TNF Blocking Agent	
	Study I		Study III		Study IV	
Response Rate	ORENCIA ^a n=32	Placebo n=32	ORENCIA ^b +MTX n=424	Placebo +MTX n=214	ORENCIA ^b +DMARDs n=256	Placebo +DMARDs n=133
ACR 20						
Month 3	53%	31%	62%***	37%	46%***	18%
Month 6	NA	NA	68%***	40%	50%***	20%
Month 12	NA	NA	73%***	40%	NA	NA
ACR 50						
Month 3	16%	6%	32%***	8%	18%**	6%
Month 6	NA	NA	40%***	17%	20%***	4%
Month 12	NA	NA	48%***	18%	NA	NA
ACR 70						
Month 3	6%	0	13%***	3%	6%*	1%
Month 6	NA	NA	20%***	7%	10%**	2%
Month 12	NA	NA	29%***	6%	NA	NA
Major Clinical Response^c	NA	NA	14%***	2%	NA	NA

* p<0.05, ORENCIA vs placebo.

** p<0.01, ORENCIA vs placebo.

*** p<0.001, ORENCIA vs placebo.

^a 10 mg/kg.

^b Dosing based on weight range (see **DOSAGE AND ADMINISTRATION**).

^c Major clinical response is defined as achieving an ACR 70 response for a continuous 6-month period.

The results of the components of the ACR response criteria for Studies III and IV are shown in Table 3. In ORENCIA-treated patients, greater improvement was seen in all ACR response criteria components through 6 and 12 months than in placebo-treated patients.

Table 3: Components of ACR Response at 6 Months

Component (median)	Inadequate Response to MTX				Inadequate Response to TNF Blocking Agent			
	Study III				Study IV			
	ORENCIA +MTX n=424		Placebo +MTX n=214		ORENCIA +DMARDs n=256		Placebo +DMARDs n=133	
	Baseline	Month 6	Baseline	Month 6	Baseline	Month 6	Baseline	Month 6
Number of tender joints (0-68)	28	7***	31	14	30	13***	31	24
Number of swollen joints (0-66)	19	5***	20	11	21	10***	20	14
Pain ^a	67	27***	70	50	73	43**	74	64
Patient global assessment ^a	66	29***	64	48	71	44***	73	63
Disability index ^b	1.75	1.13***	1.75	1.38	1.88	1.38***	2.00	1.75
Physician global assessment ^a	69	21***	68	40	71	32***	69	54
CRP (mg/dL)	2.2	0.9***	2.1	1.8	3.4	1.3***	2.8	2.3

** p<0.01, ORENCIA vs placebo, based on mean percent change from baseline.

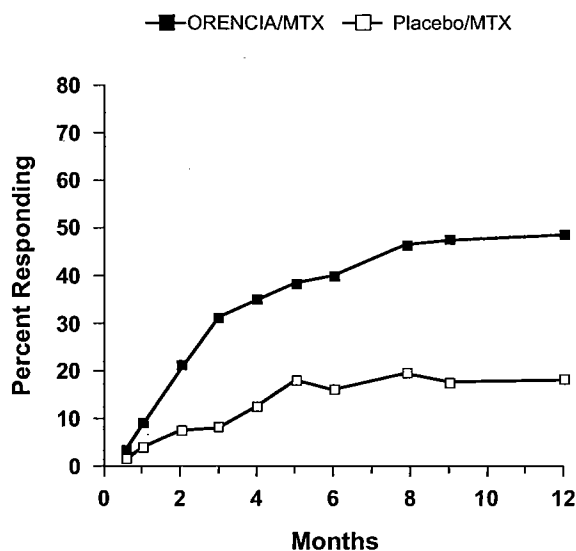
*** p<0.001, ORENCIA vs placebo, based on mean percent change from baseline.

^a Visual analog scale: 0 = best, 100 = worst.

^b Health Assessment Questionnaire¹: 0 = best, 3 = worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

The time course of ACR 50 response for Study III is shown in Figure 1. The time course for Study IV was similar.

Figure 1
Time Course of ACR 50 Response
Inadequate Response to MTX (Study III)



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

Radiographic Response

Structural joint damage was assessed radiographically and expressed as change in Genant-modified Total Sharp Score² (TSS) and its components, the erosion score and Joint Space Narrowing (JSN) score, at month 12 compared to baseline. In Study III the baseline median TSS was 31.7 in ORENCIA-treated patients and 33.4 in placebo-treated patients. The results are shown in Table 4. ORENCIA/MTX slowed the progression of structural damage compared to placebo/MTX alone.

Table 4: Mean Radiographic Changes Over 12 Months in Study III

Parameter	ORENCIA/MTX n=391	Placebo/MTX n=195	Placebo/MTX - ORENCIA/MTX (95% Confidence Interval)	P-value ^a
Total Sharp score	1.21	2.32	1.11 (0.35, 1.88)	0.012
Erosion score	0.63	1.14	0.51 (0.08, 0.94)	0.029
JSN score	0.58	1.18	0.60 (0.21, 0.99)	0.009

^a Based on non-parametric analysis.

Physical Function Response and Health-Related Outcomes

Improvement in physical function was measured by the Health Assessment Questionnaire Disability Index (HAQ-DI).^{1,3} In Studies II-V, ORENCIA demonstrated greater improvement from baseline than placebo in the HAQ-DI. The results from Studies II and III are shown in Table 5. Similar results were observed in Study V. During the open-label period of Study II, the improvement in physical function has been maintained for up to 3 years.

Table 5: Mean Improvement from Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI)

	Inadequate Response to Methotrexate			
	Study II		Study III	
	ORENCIA ^a +MTX (n=115)	Placebo +MTX (n=119)	ORENCIA ^b +MTX (n=422)	Placebo +MTX (n=212)
HAQ Disability Index				
Baseline (Mean)	0.98 ^c	0.97 ^c	1.69 ^d	1.69 ^d
Mean Improvement Year 1	0.40 ^{c***}	0.15 ^c	0.66 ^{d***}	0.37 ^d

*** p<0.001, ORENCIA vs placebo.

^a 10 mg/kg.

^b Dosing based on weight range (see **DOSAGE AND ADMINISTRATION**).

^c Modified Health Assessment Questionnaire³: 0 = best, 3 = worst; 8 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

^d Health Assessment Questionnaire¹: 0 = best, 3 = worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

Health-related quality of life was assessed by the SF-36 questionnaire⁴ at 6 months in Studies II, III, and IV and at 12 months in Studies II and III. In these studies,

improvement was observed in the ORENCIA group as compared with the placebo group in all 8 domains of the SF-36 as well as the Physical Component Summary (PCS) and the Mental Component Summary (MCS).

INDICATIONS AND USAGE

ORENCIA is indicated for reducing signs and symptoms, inducing major clinical response, slowing the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs, such as methotrexate or TNF antagonists. ORENCIA may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.

ORENCIA should not be administered concomitantly with TNF antagonists. ORENCIA is not recommended for use concomitantly with anakinra.

CONTRAINDICATIONS

ORENCIA should not be administered to patients with known hypersensitivity to ORENCIA or any of its components.

WARNINGS

Concomitant Use with TNF Antagonists

In controlled clinical trials, patients receiving concomitant ORENCIA and TNF antagonist therapy experienced more infections (63%) and serious infections (4.4%) compared to patients treated with only TNF antagonists (43% and 0.8%, respectively) (see **ADVERSE REACTIONS: Infections**). These trials failed to demonstrate an important enhancement of efficacy with concomitant administration of ORENCIA with TNF antagonist; therefore, concurrent therapy with ORENCIA and a TNF antagonist is not recommended. While transitioning from TNF antagonist therapy to ORENCIA therapy, patients should be monitored for signs of infection.

PRECAUTIONS

Hypersensitivity

Of 2688 patients treated with ORENCIA in clinical trials, there were two cases of anaphylaxis or anaphylactoid reactions. Other events potentially associated with drug

hypersensitivity, such as hypotension, urticaria, and dyspnea, each occurred in less than 0.9% of ORENCIA-treated patients. Appropriate medical support measures for the treatment of hypersensitivity reactions should be available for immediate use in the event of a reaction (see **ADVERSE REACTIONS: Infusion-Related Reactions and Hypersensitivity Reactions**).

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 (see **ADVERSE REACTIONS: Infections**). A higher rate of serious infections has been observed in patients treated with concurrent TNF antagonists and ORENCIA (see **WARNINGS: Concomitant Use with TNF Antagonists**).

Prior to initiating immunomodulatory therapies, including ORENCIA, patients should be screened for latent tuberculosis infection with a tuberculin skin test. ORENCIA has not been studied in patients with a positive tuberculosis screen, and the safety of ORENCIA in individuals with latent tuberculosis infection is unknown. Patients testing positive in tuberculosis screening should be treated by standard medical practice prior to therapy with ORENCIA.

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. The efficacy of vaccination in patients receiving ORENCIA is not known. Based on its mechanism of action, ORENCIA may blunt the effectiveness of some immunizations.

Use in Patients with Chronic Obstructive Pulmonary Disease (COPD)

COPD patients treated with ORENCIA developed adverse events more frequently than those treated with placebo, including COPD exacerbations, cough, rhonchi, and dyspnea. Use of ORENCIA in patients with rheumatoid arthritis and COPD should be undertaken

with caution and such patients should be monitored for worsening of their respiratory status (see **ADVERSE REACTIONS: Adverse Reactions in Patients with COPD**).

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.

Drug Interactions

Formal drug interaction studies have not been conducted with ORENCIA.

Population pharmacokinetic analyses revealed that MTX, NSAIDs, corticosteroids, and TNF blocking agents did not influence abatacept clearance (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**). The majority of patients in RA clinical studies received one or more of the following concomitant medications with ORENCIA: MTX, NSAIDs, corticosteroids, TNF blocking agents, azathioprine, chloroquine, gold, hydroxychloroquine, leflunomide, sulfasalazine, and anakinra.

Concurrent administration of a TNF antagonist with ORENCIA has been associated with an increased risk of serious infections and no significant additional efficacy over use of the TNF antagonists alone. Concurrent therapy with ORENCIA and TNF antagonists is not recommended (see **WARNINGS: Concomitant Use with TNF Antagonists**).

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

Immunosuppression

The possibility exists for drugs inhibiting T cell activation, including ORENCIA, to affect host defenses against infections and malignancies since T cells mediate cellular immune responses. The impact of treatment with ORENCIA on the development and course of malignancies is not fully understood (see **ADVERSE REACTIONS: Malignancies**). In clinical trials, a higher rate of infections was seen in ORENCIA-treated patients compared to placebo (see **ADVERSE REACTIONS: Infections**).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a mouse carcinogenicity study, weekly subcutaneous injections of 20, 65, or 200 mg/kg of abatacept administered each week for up to 84 weeks in males and 88 weeks in females were associated with increases in the incidence of malignant lymphomas (all doses) and mammary gland tumors (intermediate- and high-dose in females). The mice from this study were infected with murine leukemia virus and mouse mammary tumor virus. These viruses are associated with an increased incidence of lymphomas and mammary gland tumors, respectively, in immunosuppressed mice. The doses used in these studies were 0.8-, 2.0- and 3.0-fold, the human exposure at 10 mg/kg, respectively, based on AUC. The relevance of these findings to the clinical use of ORENCIA is unknown.

In a one-year toxicity study in cynomolgus monkeys, abatacept was administered intravenously once weekly at doses up to 50 mg/kg (9-fold the human exposure at 10 mg/kg dose based on AUC). Abatacept was not associated with any significant drug-related toxicity. Reversible pharmacological effects consisted of minimal transient decreases in serum IgG and minimal to severe lymphoid depletion of germinal centers in the spleen and/or lymph nodes. No evidence of lymphomas or preneoplastic morphologic changes was observed, despite the presence of a virus (lymphocryptovirus) known to cause these lesions in immunosuppressed monkeys within the time frame of this study. The relevance of these findings to the clinical use of ORENCIA is unknown.

No mutagenic potential of abatacept was observed in the *in vitro* reverse Ames or Chinese hamster ovary/hypoxanthine guanine phosphoribosyl-transferase (CHO/HGPRT) forward point mutation (with or without metabolic activation) assays, and no chromosomal aberrations were observed in human lymphocytes (with or without metabolic activation) treated with abatacept. In rats, abatacept had no adverse effects on male or female fertility at doses up to 200 mg/kg every three days (11-fold a human dose based on AUC).

Pregnancy Category C

Abatacept was found not to be teratogenic in mice at doses up to 300 mg/kg and in rats and rabbits at doses up to 200 mg/kg daily (29-fold a human 10 mg/kg dose based on AUC in rats and rabbits). Rats treated with abatacept every three days during early gestation throughout the lactation period showed no adverse effects in the offspring at doses up to 45 mg/kg (3-fold a human 10 mg/kg dose based on AUC). At a dose of

200 mg/kg (11-fold a human 10 mg/kg dose based on AUC), alterations of immune function consisted of a 9-fold increase in the T-cell dependent antibody response in female pups and inflammation of the thyroid in one female pup out of 10 males and 10 females evaluated. Whether these findings indicate a risk for development of autoimmune diseases in humans exposed *in utero* to abatacept has not been determined. Abatacept was shown to cross the placenta. Because animal reproduction studies are not always predictive of human response, ORENCIA should be used during pregnancy only if clearly needed. There are no adequate and well-controlled studies in pregnant women.

Nursing Mothers

Abatacept has been shown to be present in rat milk. It is not known whether abatacept is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ORENCIA, possibly including effects on the developing immune system, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness of ORENCIA in pediatric patients have not been established.

Geriatric Use

A total of 323 patients 65 years of age and older, including 53 patients 75 years and older, received ORENCIA in clinical studies. No overall differences in safety or effectiveness were observed between these patients and younger patients, but these numbers are too low to rule out differences. 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.

ADVERSE REACTIONS

General

The most serious adverse reactions were serious infections and malignancies (see **ADVERSE REACTIONS: Infections** and **ADVERSE REACTIONS: Malignancies**).

The most commonly reported adverse events (occurring in $\geq 10\%$ of patients treated with ORENCIA) were headache, upper respiratory tract infection, nasopharyngitis, and nausea.

The adverse events most frequently resulting in clinical intervention (interruption or discontinuation of ORENCIA) were due to infection. The most frequently reported infections resulting in dose interruption were upper respiratory tract infection (1.0%), bronchitis (0.7%), and herpes zoster (0.7%). The most frequent infections resulting in discontinuation were pneumonia (0.2%), localized infection (0.2%), and bronchitis (0.1%).

Because clinical trials are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not predict the rates observed in a broader patient population in clinical practice.

The data described herein reflect exposure to ORENCIA in patients with active RA in placebo-controlled studies (1955 patients with ORENCIA, 989 with placebo). The studies 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). A subset of these patients received concomitant biologic DMARD therapy, such as a TNF blocking agent (204 patients with ORENCIA, 134 with placebo).

Infections

In the placebo-controlled trials, infections were reported in 54% of ORENCIA-treated patients and 48% of placebo-treated patients. The most commonly reported infections (reported in 5-13% of patients) were upper respiratory tract infection, nasopharyngitis, sinusitis, urinary tract infection, influenza, and bronchitis. Other infections reported in fewer than 5% of patients at a higher frequency ($>0.5\%$) with ORENCIA compared to placebo, were rhinitis, herpes simplex, and pneumonia (see **PRECAUTIONS: Infections**).

Serious infections were reported in 3.0% of patients treated with ORENCIA and 1.9% of patients treated with placebo. The most common (0.2-0.5%) serious infections reported with ORENCIA were pneumonia, cellulitis, urinary tract infection, bronchitis, diverticulitis, and acute pyelonephritis (see **PRECAUTIONS: Infections**).

Malignancies

In the placebo-controlled portions of the clinical trials (1955 patients for a median of 12 months), the overall frequencies of malignancies were similar in the ORENCIA- and placebo-treated patients (1.3% and 1.1%, respectively). However, more cases of lung cancer were observed in ORENCIA-treated patients (4, 0.2%) than placebo-treated patients (0). In the cumulative ORENCIA clinical trials (placebo-controlled and uncontrolled, open-label) a total of 8 cases of lung cancer (0.21 cases per 100 patient-years) and 4 lymphomas (0.10 cases per 100 patient-years) were observed in 2688 patients (3827 patient-years). The rate observed for lymphoma is approximately 3.5-fold higher than expected in an age- and gender-matched general population based on the Surveillance, Epidemiology, and End Results Database.⁵ Patients with RA, particularly those with highly active disease, are at a higher risk for the development of lymphoma. Other malignancies included skin, breast, bile duct, bladder, cervical, endometrial, lymphoma, melanoma, myelodysplastic syndrome, ovarian, prostate, renal, thyroid, and uterine cancers (see **PRECAUTIONS: Immunosuppression**). The potential role of ORENCIA in the development of malignancies in humans is unknown.

Infusion-Related Reactions and Hypersensitivity Reactions

Acute infusion-related events (adverse reactions occurring 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% for ORENCIA, 6% for placebo). The most frequently reported events (1-2%) were dizziness, headache, and hypertension.

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, and dyspnea; other symptoms included nausea, flushing, urticaria, cough, hypersensitivity, pruritus, rash, and wheezing. Most of these reactions were mild to moderate. Fewer than 1% of ORENCIA-treated patients discontinued due to an acute infusion-related event. In controlled trials, 6 ORENCIA-treated patients compared to 2 placebo-treated patients discontinued study treatment due to acute infusion-related events.

Of 2688 patients treated with ORENCIA in clinical trials, there were two cases of anaphylaxis or anaphylactoid reactions. Other events potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, each occurred in less than 0.9% of ORENCIA-treated patients and generally occurred within 24 hours of ORENCIA

infusion. Appropriate medical support measures for the treatment of hypersensitivity reactions should be available for immediate use in the event of a reaction (see **PRECAUTIONS: Hypersensitivity**).

Adverse Reactions in Patients with COPD

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

Other Adverse Reactions

Adverse events occurring in 3% or more of patients and at least 1% more frequently in ORENCIA-treated patients during placebo-controlled RA studies are summarized in Table 6.

Table 6: Adverse Events Occurring in 3% or More of Patients and at Least 1% More Frequently in ORENCIA-Treated Patients During Placebo-Controlled RA Studies

Adverse Event (Preferred Term)	ORENCIA (n=1955) ^a Percentage	Placebo (n=989) ^b Percentage
Headache	18	13
Nasopharyngitis	12	9
Dizziness	9	7
Cough	8	7
Back pain	7	6
Hypertension	7	4
Dyspepsia	6	4
Urinary tract infection	6	5
Rash	4	3
Pain in extremity	3	2

^a Includes 204 patients on concomitant biologic DMARDs (adalimumab, anakinra, etanercept, or infliximab).

^b Includes 134 patients on concomitant biologic DMARDs (adalimumab, anakinra, etanercept, or infliximab).

Immunogenicity

Antibodies directed against the entire abatacept molecule or to the CTLA-4 portion of abatacept were assessed by ELISA assays in RA patients for up to 2 years following repeated treatment with ORENCIA. Thirty-four of 1993 (1.7%) patients developed binding antibodies to the entire abatacept molecule or to the CTLA-4 portion of abatacept. Because trough levels of abatacept can interfere with assay results, a subset analysis was performed. In this analysis it was observed that 9 of 154 (5.8%) patients that had discontinued treatment with ORENCIA for over 56 days developed antibodies.

Samples with confirmed binding activity to CTLA-4 were assessed for the presence of neutralizing antibodies in a cell-based luciferase reporter assay. Six of 9 (67%) evaluable patients were shown to possess neutralizing antibodies.

No correlation of antibody development to clinical response or adverse events was observed.

The data reflect the percentage of patients whose test results were positive for antibodies to abatacept in specific assays, and are highly dependent on the sensitivity and specificity of the assays. Additionally, the observed incidence of antibody positivity in an assay may

be influenced by several factors, including sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to abatacept with the incidence of antibodies to other products may be misleading.

OVERDOSAGE

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.

DOSAGE AND ADMINISTRATION

ORENCIA should be administered as a 30-minute intravenous infusion at the dose specified in Table 7. Following the initial administration, ORENCIA should be given at 2 and 4 weeks after the first infusion, then every 4 weeks thereafter. ORENCIA may be used as monotherapy or concomitantly with disease-modifying, anti-rheumatic drugs (DMARDs) other than TNF antagonists.

Table 7: Dose of ORENCIA

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.

Preparation and Administration Instructions

Use aseptic technique.

ORENCIA is provided as a lyophilized powder in preservative-free, single-use vials. Refer to Table 7 for the dose and number of ORENCIA vials required. Each ORENCIA vial provides 250 mg of abatacept for administration. The ORENCIA powder in each vial must be reconstituted with 10 mL of Sterile Water for Injection, USP, using **ONLY the SILICONE-FREE DISPOSABLE SYRINGE PROVIDED WITH EACH VIAL** and an 18-21 gauge needle. If the ORENCIA powder is accidentally reconstituted using a

siliconized syringe, the solution may develop a few translucent particles. Discard any solutions prepared using siliconized syringes.

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 1-800-ORENCIA™.

During reconstitution, 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.

- 1) To reconstitute the ORENCIA powder, remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of Sterile Water for Injection, USP, to the glass wall of the vial. Do not use the vial if the vacuum is not present. Rotate the vial with gentle swirling until the contents are completely dissolved.
- 2) Upon complete dissolution of the lyophilized powder, the vial should be vented with a needle to dissipate any foam that may be present. After reconstitution, each milliliter will contain 25 mg (250 mg/10 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, USP, equal to the volume of the reconstituted ORENCIA vials (for 2 vials remove 20 mL, for 3 vials remove 30 mL, for 4 vials remove 40 mL). Slowly add the reconstituted ORENCIA solution from each vial into the infusion bag or bottle using the same **SILICONE-FREE DISPOSABLE SYRINGE PROVIDED WITH EACH VIAL**. Gently mix. The concentration of the fully diluted ORENCIA solution in the infusion bag or bottle will be approximately 5, 7.5, or 10 mg of abatacept per mL of solution depending on whether 2, 3, or 4 vials of ORENCIA are used. 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 μm to 1.2 μm).
- 6) The infusion of the fully diluted ORENCIA solution must be completed within 24 hours of reconstitution of the ORENCIA vials. The fully diluted ORENCIA solution may be stored at room temperature or refrigerated at 2°C to 8°C (36°F to 46°F) before use.
- 7) 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 coadministration of ORENCIA with other agents.

Storage and Stability

ORENCIA lyophilized powder must be refrigerated at 2°C to 8°C (36°F to 46°F). Do not use beyond the expiration date. Protect the vials from light by storing in the original package until time of use.

HOW SUPPLIED

ORENCIA lyophilized powder for intravenous infusion is supplied as an individually packaged, single-use vial with a silicone-free disposable syringe. The product is available in the following strength:

NDC 0003-2187-10 providing 250 mg of abatacept in a 15-mL vial.

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ORENCIA[®]
(abatacept)

Rx only

Patient Information

This leaflet tells you about ORENCIA (pronounced oh-REN-see-ah). Please read this information before you start using ORENCIA and each time before you are scheduled to receive ORENCIA, in case something has changed. The information in this leaflet does not take the place of talking with your doctor before you start receiving this medicine and at check ups. Talk to your doctor if you have any questions about your treatment with ORENCIA.

What is ORENCIA?

ORENCIA is a medicine that is used to treat adults with moderate to severe rheumatoid arthritis (RA) who have not been helped by other medicines for RA. RA is a disease that

causes pain and joint inflammation (tenderness and swelling). RA can also cause joint damage. Your doctor has decided to treat you with ORENCIA because your disease is still active even though you may have tried other treatments.

How does ORENCIA work?

ORENCIA is a medicine that keeps the immune system from attacking healthy tissues in the body. The immune system defends the body against infections caused by bacteria and viruses. A normal immune system leaves healthy body tissues alone. In people with RA, the immune system attacks normal body tissues causing damage and inflammation especially in the tissues of your joints. ORENCIA interferes with an important step in this attack. By decreasing the immune system's attack on normal tissues, ORENCIA can reduce pain and joint inflammation, and slow the damage to your bones and cartilage. However, ORENCIA can also lower your body's ability to fight infection. ORENCIA treatment can make you more prone to getting infections or make any infection you have worse. It is important to tell your doctor if you think you have any infections.

Who should not receive ORENCIA?

You should not receive ORENCIA if you have ever had an allergic reaction to ORENCIA.

What should I tell my doctor before treatment with ORENCIA?

Before you receive treatment with ORENCIA you should tell your doctor if you:

- are taking a TNF blocker to treat RA. You may have a higher chance of getting a serious infection if you take ORENCIA with other biologic medications for RA.
- have any kind of infection including an infection that is in only one place in your body (such as an open cut or sore), or an infection that is in your whole body (such as the flu). Having an infection could put you at risk for serious side effects from ORENCIA. If you are unsure, please ask your doctor.
- have an infection that won't go away or a history of infections that keep coming back.
- have had tuberculosis (TB), a positive skin test for TB, or if you recently have been in close contact with someone who has had TB. If you develop any of the symptoms of TB (a dry cough that doesn't go away, weight loss, fever, night sweats) call your doctor right away. Before you start ORENCIA, your doctor may examine you for TB or perform a skin test.
- are scheduled to have surgery.
- recently received a vaccination or are scheduled for any vaccination.

- are pregnant or planning to become pregnant. It is not known if ORENCIA can harm your unborn baby.
- are breastfeeding. ORENCIA can pass into breast milk. You will need to decide to either breastfeed or receive treatment with ORENCIA, but not both.

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

What important information do I need to know about side effects with ORENCIA?

Like all medicines that affect your immune system, ORENCIA can cause serious side effects. The possible serious side effects include:

- **Serious infections.** Patients taking ORENCIA are at increased risk for developing infections including pneumonia, and other infections caused by viruses, bacteria, or fungi. Call your doctor immediately if you feel sick or get any infection during treatment with ORENCIA.
- **Allergic reactions.** These reactions are usually mild or moderate and include hives, swollen face, eyelids, lips, tongue, throat, or trouble breathing.
- **Malignancies.** There have been rare cases of certain kinds of cancer in patients receiving ORENCIA. The role of ORENCIA in the development of cancer is not known.

What are the more common side effects with ORENCIA?

- The more common side effects with ORENCIA are headache, upper respiratory tract infection, sore throat, and nausea.

Can I receive ORENCIA if I am pregnant or breast-feeding?

ORENCIA has not been studied in pregnant women or nursing mothers, so we don't know what the effects are on pregnant women or nursing babies. You should tell your doctor if you are pregnant, become pregnant, or are thinking about becoming pregnant.

Can I receive ORENCIA if I am taking other medicines for my RA or other conditions?

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

tell your doctor. Taking ORENCIA with TNF blocker medications (Enbrel[®], Humira[®], Remicade[®]) is not recommended.

How will ORENCIA be given to me?

ORENCIA will be given to you by a healthcare professional using an IV. This means the medicine will be given to you through a needle placed in a vein in your arm. It will take about 30 minutes to give you the full dose of medicine.

How often will I receive ORENCIA

You will receive your first dose of ORENCIA followed by additional doses at 2 and 4 weeks after the first dose. You will then receive a dose every 4 weeks.

What should I do if I miss a dose of ORENCIA?

If you miss receiving ORENCIA when you are supposed to, ask your doctor when to schedule your next dose.

What if I still have questions?

If you have any questions or problems, always talk with your doctor. You can also call 1-800-ORENCIA[™] toll-free or visit the ORENCIA internet site at www.ORENCIA.com or the company internet site at www.BMS.com.

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