ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ORENCIA 250 mg powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 250 mg of abatacept.
Each ml contains 25 mg of abatacept, after reconstitution.

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

Excipient: sodium: 0.375 mmol per vial

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

The powder is a white to off-white whole or fragmented cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis.

Adults
To be administered as a 30-minute intravenous infusion at the dose specified in Table 1. Following the initial administration, ORENCIA should be given 2 and 4 weeks after the first infusion, then every 4 weeks thereafter.

Table 1: Dose of ORENCIA[a]

Body Weight of Patient	Dose	Number of Vials[b]
< 60 kg	500 mg	2
≥ 60 kg to ≤ 100 kg	750 mg	3
> 100 kg	1,000 mg	4

[a] Approximating 10 mg/kg.
[b] Each vial provides 250 mg of abatacept for administration.

Each vial of ORENCIA 250 mg must be reconstituted with 10 ml of water for injections, using the silicone-free syringe provided. The reconstituted solution must then be diluted to 100 ml with sodium chloride 9 mg/ml (0.9%) solution for injection, before administration by intravenous infusion (see section 6.6).

No dose adjustment is required when used in combination with other DMARDs, corticosteroids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics.

If a response to abatacept is not present within 6 months of treatment, the potential benefits of continuing treatment, known and potential risks, and therapeutic alternatives should be considered (see section 5.1).

Elderly patients
No dose adjustment is required.

Paediatric patients
There is no experience in children or adolescents. As a result, the use of ORENCIA in children or adolescents is not recommended until further data become available.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Severe and uncontrolled infections such as sepsis and opportunistic infections (see section 4.4).

4.4 Special warnings and precautions for use

Combination with TNF blocking agents
There is limited experience with use of abatacept in combination with TNF blocking agents (see section 5.1). In placebo-controlled clinical trials, in comparison with patients treated with TNF blocking agents and placebo, patients who received combination TNF blocking agents with abatacept experienced an increase in overall infections and serious infections (see section 4.5). Abatacept is not recommended for use in combination with TNF blocking agents.

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

Allergic reactions
Allergic reactions have been reported uncommonly with abatacept administration in clinical trials, where patients were not required to be pretreated to prevent allergic reactions (see section 4.8). Special caution should be exercised in patients with a history of allergic reactions to abatacept or to any of the excipients. If any serious allergic or anaphylactic reaction occurs, ORENCIA therapy should be discontinued immediately and appropriate therapy initiated.

Effects on the immune system
Medicinal products which affect the immune system, including ORENCIA, may affect host defences against infections and malignancies, and affect vaccination responses.

Co-administration of ORENCIA with biologic immunosuppressive or immunomodulatory agents could potentiate the effects of ORENCIA on the immune system. There is insufficient evidence to assess the safety and efficacy of ORENCIA in combination with anakinra or rituximab.

Infections
Serious infections have been reported with abatacept (see section 4.8). Treatment with ORENCIA should not be initiated in patients with active infections until infections are controlled. Physicians should exercise caution when considering the use of ORENCIA in patients with a history of recurrent infections or underlying conditions which may predispose them to 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.

No increase of tuberculosis was observed in the pivotal placebo-controlled studies. Nevertheless, patients should be screened for latent tuberculosis prior to initiating ORENCIA. The available medical guidelines should also be taken into account.

Anti-rheumatic therapies have been associated with hepatitis B reactivation. Therefore, screening for viral hepatitis should be performed in accordance with published guidelines before starting therapy with ORENCIA.

Malignancies
In the placebo-controlled clinical trials, the frequencies of malignancies in abatacept- and placebo-treated patients were 1.4% and 1.1%, respectively (see section 4.8). Patients with known malignancies were not included in these clinical trials. In carcinogenicity studies in mice, an increase in lymphomas and mammary tumours were noted. The clinical significance of this observation is unknown (see section 5.3). The potential role of ORENCIA in the development of malignancies, including lymphoma, in humans is unknown.

Vaccinations
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. Insufficient data are available on the effects of vaccinations in patients receiving ORENCIA. Medicinal products that affect the immune system, including ORENCIA, may blunt the effectiveness of some immunisations.

Elderly patients
A total of 323 patients 65 years of age and older, including 53 patients 75 years and older, received abatacept in placebo-controlled clinical trials. Similar efficacy was observed in these patients and in younger patients. The frequencies of serious infection and malignancy relative to placebo among abatacept-treated patients over age 65 were higher than among those under age 65. Because there is a higher incidence of infections and malignancies in the elderly in general, caution should be used when treating the elderly (see section 4.8).

Autoimmune processes
There is a theoretical concern that treatment with ORENCIA might increase the risk for autoimmune processes, for example deterioration of multiple sclerosis. In the placebo-controlled clinical trials, abatacept treatment did not lead to increased autoantibody formation, such as antinuclear and anti-dsDNA antibodies, relative to placebo treatment (see section 4.8).

Blood glucose testing
Parenteral medicinal 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 nicotine adenine dinucleotide (GDH-NAD), glucose oxidase, or glucose hexokinase test methods.

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

4.5 Interaction with other medicinal products and other forms of interaction

Combination with TNF blocking agents
There is limited experience with the use of abatacept in combination with TNF blocking agents (see section 5.1). While TNF blocking agents did not influence abatacept clearance, in placebo-controlled clinical trials, patients receiving concomitant treatment with abatacept and TNF blocking agents experienced more infections and serious infections than patients treated with only TNF blocking agents. Therefore, concurrent therapy with ORENCIA and a TNF blocking agent is not recommended.

Combination with other medicinal products
Population pharmacokinetic analyses did not detect any effect of methotrexate, NSAIDs, and corticosteroids on abatacept clearance (see section 5.2).
No major safety issues were identified with use of abatacept in combination with sulfasalazine, hydroxychloroquine, or leflunomide.

See section 4.4 regarding combination with other medicinal products that affect the immune system and with vaccinations.

4.6 Pregnancy and lactation

There are no adequate data from use of abatacept in pregnant women. In embryo-foetal development studies no undesirable effects were observed at doses up to 29-fold a human 10 mg/kg dose based on AUC. In a pre- and postnatal development study limited changes in immune function were observed at 11-fold a human 10 mg/kg dose based on AUC (see section 5.3). ORENCIA should not be used in pregnant women unless clearly necessary. Women of child-bearing potential should use effective contraception during treatment with ORENCIA and up to 14 weeks after the last dose of abatacept treatment.

Use during lactation
Abatacept has been shown to be present in rat milk. It is not known whether abatacept is excreted in human milk. Women should not breastfeed while treated with ORENCIA and for up to 14 weeks after the last dose of abatacept treatment.

Fertility
Formal studies of the potential effect of ORENCIA on human fertility have not been conducted.
In rats, abatacept had no undesirable effects on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Abatacept has been studied in patients with active rheumatoid arthritis in placebo-controlled clinical trials (1,955 patients with abatacept, 989 with placebo). The trials had either a double-blind, placebo-controlled period of 6 months (258 patients with abatacept, 133 with placebo) or 1 year (1,697 patients with abatacept, 856 with placebo). Most patients in these trials were taking methotrexate (81.9% with abatacept, 83.3% with placebo). Other concomitant medications included: NSAIDs (83.9% with abatacept, 85.1% with placebo); systemic corticosteroids (74.7% with abatacept, 75.8% with placebo); non-biological DMARD therapy, most commonly chloroquine/hydroxychloroquine, leflunomide and/or sulfasalazine (26.9% with abatacept, 32.1% with placebo); TNF blocking agents, mainly etanercept (9.4% with abatacept, 12.3% with placebo); and anakinra (1.1% with abatacept, 1.6% with placebo).

In placebo-controlled clinical trials with abatacept, adverse drug reactions (ADRs) were reported in 52.2% of abatacept-treated patients and 46.1% of placebo-treated patients. The most frequently reported adverse drug reactions (≥ 5%) among abatacept-treated patients were headache and nausea.

The proportion of patients who discontinued treatment due to ADRs was 3.4% for abatacept-treated patients and 2.2% for placebo-treated patients.

Listed in Table 2 are adverse drug reactions that occurred with greater frequency (difference > 0.2%) in abatacept-treated patients than in placebo-treated patients. The list is presented by system organ class and frequency, using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2: Undesirable Effects in Placebo-Controlled Trials

Investigations	Common	Blood pressure increased, liver function test abnormal (including transaminases increased)
	Uncommon	Blood pressure decreased, weight increased
Cardiac disorders	Uncommon	Tachycardia, bradycardia, palpitations
Blood and lymphatic system disorders	Uncommon	Thrombocytopenia, leukopenia
Nervous system disorders	Very Common	Headache
	Common	Dizziness
	Uncommon	Paraesthesia
Eye disorders	Uncommon	Conjunctivitis, visual acuity reduced
Ear and labyrinth disorders	Uncommon	Vertigo
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 and connective tissue disorders	Uncommon	Arthralgia, pain in extremity
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, onychomycosis

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Uncommon	Basal cell carcinoma
Vascular disorders	Common Uncommon	Hypertension, flushing Hypotension, hot flush
General disorders and administration site conditions	Common Uncommon	Fatigue, asthenia Influenza like illness
Reproductive system and breast disorders	Uncommon	Amenorrhea
Psychiatric disorders	Uncommon	Depression, anxiety

ADRs reported in abatacept-treated patients which did not occur with an excess incidence (i.e. the difference was not > 0.2%) over placebo but were considered to be medically relevant include the following events:

Common: herpes zoster;
Uncommon: pneumonia, hypersensitivity, pyelonephritis, bronchospasm, urticaria, psoriasis, cystitis, migraine, throat tightness, dry eye;
Rare: sepsis, bacteraemia.

Additional information

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

Serious infections at least possibly related to treatment were reported in 1.8% of abatacept-treated patients and 1.0% of placebo-treated patients. Serious infections reported in at least one patient treated with abatacept (0.05% of patients) included the following: pneumonia; bronchitis; cellulitis; acute pyelonephritis; urinary tract infection; diverticulitis, intestinal abscess; localised infection; skin abscess; musculoskeletal infections; sepsis; empyema; hepatitis E; and tuberculosis (see section 4.4).

Malignancies
In placebo-controlled clinical trials, malignancies were reported in 27 of 1,955 abatacept-treated patients observed during 1,687 patient-years, and in 11 of 989 placebo-treated patients observed during 794 patient-years.

In double-blind and open-label clinical trials, malignancies were reported in 66 of 2,688 abatacept-treated patients during 4,764 patient-years. This included 33 patients with non-melanoma skin cancers, 28 with solid organ cancers, and 6 with hematologic malignancies (4 with lymphomas and 2 with myelodysplastic syndromes). The most commonly reported solid organ cancer was lung cancer (11 cases). 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 number of observed malignancies was consistent with that expected in an age- and gender-matched rheumatoid arthritis population (see section 4.4).

Infusion-related reactions
Acute infusion-related events (adverse reactions occurring within 1 hour of the start of the infusion) in Studies II, III, and IV (see section 5.1) were more common in the abatacept-treated patients than the

placebo-treated patients (9.8% for abatacept, 6.7% for placebo). The most frequently reported events with abatacept (1-2%) were dizziness, headache, and hypertension.

Acute infusion-related events that were reported in > 0.1% and ≤ 1% of patients treated with abatacept 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.

Hypersensitivity reactions were uncommon. In 2,688 abatacept-treated patients during 4,764 patient-years, there was 1 case of anaphylaxis. Other events potentially associated with hypersensitivity to the medicinal product, such as hypotension, urticaria, and dyspnea, each occurred in less than 0.6% of abatacept-treated patients.

Discontinuation due to an acute infusion-related reaction occurred in 0.4% of patients receiving abatacept and in 0.2% of placebo-treated patients.

Adverse drug reactions in patients with chronic obstructive pulmonary disease (COPD)
In Study IV, there were 37 patients with COPD treated with abatacept and 17 treated with placebo. The COPD patients treated with abatacept developed adverse drug reactions more frequently than those treated with placebo (51.4% vs. 47.1%, respectively). Respiratory disorders occurred more frequently in abatacept-treated patients than in placebo-treated patients (10.8% vs. 5.9%, respectively); these included COPD exacerbation, and dyspnea. A greater percentage of abatacept- 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
Abatacept therapy did not lead to increased formation of autoantibodies, i.e., antinuclear and anti-dsDNA antibodies, compared with placebo.

Immunogenicity
Antibodies directed against the abatacept molecule were assessed by ELISA assays in rheumatoid arthritis patients treated for up to 3 years with abatacept. Sixty-two of 2,237 (2.8%) patients developed binding antibodies. In patients assessed for antibodies at least 56 days after discontinuation of abatacept, 15 of 203 (7.4%) developed antibodies.

Samples with confirmed binding activity to CTLA-4 were assessed for the presence of neutralizing antibodies. Eight of 13 evaluable patients were shown to possess neutralizing antibodies.

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. The potential clinical relevance of neutralizing antibody formation is not known. Because immunogenicity analyses are product-specific, comparison of antibody rates with those from other products is not appropriate.

Safety information related to the pharmacological class
Abatacept is the first selective co-stimulation modulator. Information on the relative safety in a clinical trial versus infliximab is summarized in section 5.1.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: selective immunosuppressants, ATC code: L04AA24

Abatacept is a fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to a modified Fc portion of human immunoglobulin G1 (IgG1). Abatacept is produced by recombinant DNA technology in Chinese hamster ovary cells.

Mechanism of action
Abatacept selectively modulates a key costimulatory signal required for full activation of T lymphocytes expressing CD28. 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 selectively inhibits this costimulatory pathway by specifically binding to CD80 and CD86. Studies indicate that naive T lymphocyte responses are more affected by abatacept than memory T lymphocyte responses.

Studies *in vitro* and in animal models demonstrate that abatacept modulates T lymphocyte-dependent antibody responses and inflammation. *In vitro*, abatacept attenuates human T lymphocyte activation as measured by decreased proliferation and cytokine production. Abatacept decreases antigen specific TNFα, interferon-γ, and interleukin-2 production by T lymphocytes.

Pharmacodynamic effects
Dose-dependent reductions were observed with abatacept in serum levels of soluble interleukin-2 receptor, a marker of T lymphocyte activation; serum interleukin-6, a product of activated synovial macrophages and fibroblast-like synoviocytes in rheumatoid arthritis; 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 remodelling, were decreased. Reductions in serum TNFα were also observed.

Clinical efficacy and safety
The efficacy and safety of abatacept were assessed in randomised, double-blind, placebo-controlled clinical trials in adult patients with active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR) criteria. Studies I, II, III, and V required patients to have at least 12 tender and 10 swollen joints at randomization. Study IV did not require any specific number of tender or swollen joints.

In Studies I, II, and V the efficacy and safety of abatacept compared to placebo were assessed in patients with an inadequate response to methotrexate and who continued on their stable dose of methotrexate. In addition, Study V investigated the safety and efficacy of abatacept or infliximab relative to placebo. In Study III the efficacy and safety of abatacept 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 IV primarily assessed safety in patients with active rheumatoid arthritis requiring additional intervention in spite of current therapy with non-biological and/or biological DMARDs; all DMARDs used at enrollment were continued.

Study I patients were randomized to receive abatacept 2 or 10 mg/kg or placebo for 12 months. Study II, III, and IV patients were randomized to receive a fixed dose approximating 10 mg/kg of abatacept or placebo for 12 (Studies II and IV) or 6 months (Study III). The dose of abatacept 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. Study V patients were randomized to receive this same fixed dose of abatacept or 3 mg/kg infliximab or placebo for 6 months. Study V continued for an additional 6 months with the abatacept and infliximab groups only.

Studies I, II, III, IV, and V evaluated 339, 638, 389, 1,441, and 431 patients, respectively.

Clinical response

ACR response
The percent of abatacept-treated patients achieving ACR 20, 50, and 70 responses in Study II (patients with inadequate response to methotrexate) and Study III (patients with inadequate response to TNF blocking agent) are shown in Table 3.

In abatacept-treated patients in Studies II and III, statistically significant improvement in the ACR 20 response versus placebo was observed after administration of the first dose (day 15), and this improvement remained significant for the duration of the studies. In Study II, 43% of the patients who had not achieved an ACR 20 response at 6 months developed an ACR 20 response at 12 months.

Table 3: ACR Responses in Placebo-Controlled Trials

	Percent of Patients			
	Inadequate Response to Methotrexate (MTX)		**Inadequate Response to TNF Blocking Agent**	
	Study II		**Study III**	
Response Rate	Abatacept[a] +MTX n = 424	Placebo +MTX n = 214	Abatacept[a] + DMARDs[b] n = 256	Placebo + DMARDs[b] n = 133
ACR 20				
Day 15	23%*	14%	18%**	5%
Month 6	68%***	40%	50%***	20%
Month 12	73%***	40%	NA[d]	NA[d]
ACR 50				
Month 6	40%***	17%	20%***	4%
Month 12	48%***	18%	NA[d]	NA[d]
ACR 70				
Month 6	20%***	7%	10%**	2%
Month 12	29%***	6%	NA[d]	NA[d]
Major Clinical Response[c]	14%***	2%	NA[d]	NA[d]

* $p < 0.05$, abatacept vs. placebo.
** $p < 0.01$, abatacept vs. placebo.
*** $p < 0.001$, abatacept vs. placebo.
[a] Fixed dose approximating 10 mg/kg (see section 4.2).
[b] Concurrent DMARDs included one or more of the following: methotrexate, chloroquine/hydroxychloroquine, sulfasalazine, leflunomide, azathioprine, gold, and anakinra.
[c] Major clinical response is defined as achieving an ACR 70 response for a continuous 6-month period.
[d] After 6 months, patients were given the opportunity to enter an open-label study.

In the open-label extension of Studies I, II, and III durable and sustained ACR 20, 50, and 70 responses have been observed through 48, 24, and 18 months, respectively, of abatacept treatment. In study I, ACR 20 responses were observed in 71% (42/59) of patients, ACR 50 in 41% (24/59), and ACR 70 in 31% (18/58) at 48 months. In study II, ACR 20 responses were observed in 88% (291/332) of patients, ACR 50 in 62% (205/332), and ACR 70 in 38% (127/334) at 24 months. In study III, ACR 20 responses were observed in 70% (118/167) of patients, ACR 50 in 43% (73/168), and ACR 70 in 22% (37/169) at 18 months.

Greater improvements were seen with abatacept than with placebo in other measures of rheumatoid arthritis disease activity not included in the ACR response criteria, such as morning stiffness.

DAS28 response
Disease activity was also assessed using the Disease Activity Score 28 (DAS28 ESR). There was a significant improvement of DAS in Studies II, III, and V as compared to placebo.

Study V: 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 V). 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. 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. The ACR responses in Study V were consistent with the DAS28 score. Further improvement was observed at 12 months with abatacept. At 6 months, the incidence of AE of infections were 48.1% (75), 52.1% (86), and 51.8% (57) and the incidence of serious AE of infections were 1.3% (2), 4.2% (7), and 2.7% (3) for abatacept, infliximab and placebo groups, respectively. At 12 months, the incidence of AE of infections were 59.6% (93), 68.5% (113), and the incidence of serious AE of infections were 1.9% (3) and 8.5% (14) for abatacept and infliximab groups, respectively.

Radiographic response
Structural joint damage was assessed radiographically over a two-year period in Study II. 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 abatacept-treated patients and 33.4 in placebo-treated patients. Abatacept/methotrexate reduced the rate of progression of structural damage compared to placebo/methotrexate after 12 months of treatment as shown in Table 4. The rate of progression of structural damage in year 2 was significantly lower than that in year 1 for patients randomized to abatacept ($p < 0.0001$).

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

Parameter	Abatacept/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.

Physical function response
Improvement in physical function was measured by the Health Assessment Questionnaire Disability Index (HAQ-DI) in Studies II, III, IV and V and the modified HAQ-DI in Study I. The results from Studies II and III are shown in Table 5.

Table 5: Improvement in Physical Function in Placebo-Controlled Trials

	Inadequate Response to Methotrexate		Inadequate Response to TNF Blocking Agent	
	Study II		Study III	
HAQ[c] Disability Index	Abatacept[a] +MTX	Placebo +MTX	Abatacept[a] +DMARDs[b]	Placebo +DMARDs[b]
Baseline (Mean)	1.69 (n = 422)	1.69 (n = 212)	1.83 (n = 249)	1.82 (n = 130)
Mean Improvement from Baseline				
Month 6	0.59*** (n = 420)	0.40 (n = 211)	0.45*** (n = 249)	0.11 (n = 130)
Month 12	0.66*** (n = 422)	0.37 (n = 212)	NA[e]	NA[e]
Proportion of patients with a clinically meaningful improvement[d]				
Month 6	61%***	45%	47%***	23%
Month 12	64%***	39%	NA[e]	NA[e]

*** $p < 0.001$, abatacept vs. placebo.

[a] Fixed dose approximating 10 mg/kg (see section 4.2).

[b] Concurrent DMARDs included one or more of the following: methotrexate, chloroquine/hydroxychloroquine, sulfasalazine, leflunomide, azathioprine, gold, and anakinra.

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

[d] Reduction in HAQ-DI of ≥ 0.3 units from baseline.

[e] After 6 months, patients were given the opportunity to enter into an open-label study.

In Study II, among patients with clinically meaningful improvement at month 12, 88% retained the response at month 18, and 85% retained the response at month 24. During the open-label period of Studies I, II, and III, the improvement in physical function has been maintained through 48, 24, and 18 months, respectively.

Health-related outcomes and quality of life

Health-related quality of life was assessed by the SF-36 questionnaire at 6 months in Studies I, II, and III and at 12 months in Studies I and II. In these studies, clinically and statistically significant improvement was observed in the abatacept 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 and the Mental Component Summary.

5.2 Pharmacokinetic properties

After multiple intravenous infusions (days 1, 15, 30, and every 4 weeks thereafter), the pharmacokinetics of abatacept in rheumatoid arthritis patients showed dose-proportional increases of C_{max} and AUC over the dose range of 2 mg/kg to 10 mg/kg. At 10 mg/kg, the mean terminal half-life was 13.1 days, ranging from 8 to 25 days. The mean distribution volume (Vss) was 0.07 l/kg and ranged from 0.02 to 0.13 l/kg. The systemic clearance was approximately 0.22 ml/h/kg. Mean steady-state trough concentrations were approximately 25 µg/ml, and mean C_{max} concentrations were approximately 290 µg/ml. No systemic accumulation of abatacept occurred upon continued repeated treatment with 10 mg/kg at monthly intervals in rheumatoid arthritis patients.

Population pharmacokinetic analyses 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. Methotrexate, NSAIDs, corticosteroids, and TNF blocking agents were not found to influence abatacept clearance.

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

5.3 Preclinical safety data

No mutagenicity or clastogenicity was observed with abatacept in a battery of *in vitro* studies. In a mouse carcinogenicity study, increases in the incidence of malignant lymphomas and mammary gland tumours (in females) occurred. The increased incidence of lymphomas and mammary tumours observed in mice treated with abatacept may have been associated with decreased control of murine leukaemia virus and mouse mammary tumour virus, respectively, in the presence of long-term immunomodulation. In a one-year toxicity study in cynomolgus monkeys, abatacept was not associated with any significant toxicity. Reversible pharmacological effects consisted of minimal transient decreases in serum IgG and minimal to severe lymphoid depletion of germinal centres in the spleen and/or lymph nodes. No evidence of lymphomas or preneoplastic morphological changes was observed, despite the presence of a virus, lymphocryptovirus, which is known to cause such lesions in immunosuppressed monkeys within the time frame of this study. The relevance of these findings to the clinical use of ORENCIA is unknown.

In rats, abatacept had no undesirable effects on male or female fertility. Embryo-foetal development studies were conducted with abatacept in mice, rats, and rabbits at doses up to 20 to 30 times a human 10 mg/kg dose and no undesirable effects were observed in the offspring. In rats and rabbits, abatacept exposure was up to 29-fold a human 10 mg/kg exposure based on AUC. Abatacept was shown to cross the placenta in rats and rabbits. In a pre- and postnatal development study with abatacept in rats, no undesirable effects were observed in pups of dams given abatacept at doses up to 45 mg/kg, representing 3-fold a human 10 mg/kg exposure based on AUC. At a dose of 200 mg/kg, representing 11-fold a human exposure at 10 mg/kg based on AUC, limited changes in immune function (a 9-fold increase in the mean T-cell-dependent antibody response in female pups and inflammation of the thyroid of 1 female pup out of 10 male and 10 female pups evaluated at this dose) were observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maltose
Sodium dihydrogen phosphate monohydrate
Sodium chloride

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. ORENCIA should not be infused concomitantly in the same intravenous line with other medicinal products.
ORENCIA should NOT be used with siliconised syringes (see section 6.6).

6.3 Shelf life

Unopened vial: 2 years

After reconstitution: chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8°C. From a microbiological point of view, the reconstituted solution should be diluted immediately.

After dilution: when the reconstituted solution is diluted immediately, the chemical and physical in-use stability of the diluted infusion solution has been demonstrated for 24 hours at 2°C - 8°C. From a microbiological point of view, the product should be used immediately.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Store in the original package in order to protect from light.
For storage conditions of the reconstituted product see section 6.3.

6.5 Nature and contents of container

250 mg powder in a vial (Type 1 glass) with a stopper (halobutyl-rubber) and flip off seal (aluminium) with a silicone-free syringe (polyethylene).

Packs of 1, 2, or 3 vials (each 15 ml) and 1, 2, or 3 silicone-free syringes, respectively.

Not all pack-sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution and dilution should be performed in accordance with good practices rules, particularly with respect to asepsis.

Reconstitution
1. Determine the dose and the number of ORENCIA vials needed (see section 4.2).

2. Under aseptic conditions, reconstitute each vial with 10 ml of water for injections, using the **silicone free-disposable syringe provided with each vial** (see section 6.2) and an 18-21 gauge needle.
- Remove the flip-top from the vial and wipe the top with an alcohol swab.
- Insert the syringe needle into the vial through the centre of the rubber stopper and direct the stream of water for injections to the glass wall of the vial.
- Do not use the vial if the vacuum is not present.
- Remove the syringe and needle after 10 ml of water for injections have been injected into the vial.
- To minimise foam formation in solutions of ORENCIA, the vial should be rotated with gentle swirling until the contents are completely dissolved. **Do not shake**. Avoid prolonged or vigorous agitation.
- Upon complete dissolution of the powder, the vial should be vented with a needle to dissipate any foam that may be present.
- After reconstitution the solution should be clear and colourless to pale yellow. Do not use if opaque particles, discolouration, or other foreign particles are present.

Dilution
3. Immediately after reconstitution, the product must be further diluted to 100 ml with sodium chloride 9 mg/ml (0.9%) solution for injection.
- From a 100 ml infusion bag or bottle, withdraw a volume of sodium chloride 9 mg/ml (0.9%) solution for injection equal to the volume of the reconstituted 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 to 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 abatacept are used.
- Any unused portion in the vials must be immediately discarded in accordance with local requirements.

4. When reconstitution and dilution are performed under aseptic conditions ORENCIA infusion solution can be used immediately or within 24 hours if stored refrigerated at 2°C to 8°C. Prior to administration, the ORENCIA solution should be inspected visually for particulate matter and discolouration. Discard the solution if any particulate matter or discolouration is observed. 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).
- Do not store any unused portion of the infusion solution for reuse.

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

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Bristol-Myers Squibb Company
6000 Thompson Road, East Syracuse
New York 13057
USA

Lonza Biologics Inc.
101 International Drive
Portsmouth, NH 03801-2815
USA

Name and address of the manufacturer responsible for batch release

Bristol-Myers Squibb S.R.L.
Contrada Fontana del Ceraso
03012 Anagni
Italy

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription. (See Annex I: Summary of Product Characteristics, section 4.2).

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

The CHMP considered that a Patient Alert Card should be provided and this is included in Annex III.

- **OTHER CONDITIONS**

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market.

Risk Management plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan.

An updated Risk Management Plan should be provided as per CHMP Guideline on Risk Management Systems for medicinal products for human use.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ORENCIA 250 mg powder for concentrate for solution for infusion
Abatacept

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 250 mg abatacept.

3. LIST OF EXCIPIENTS

Excipients: maltose, sodium dihydrogen phosphate monohydrate and sodium chloride

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion

1 vial
1 sterile silicone-free syringe

2 vials
2 sterile silicone-free syringes

3 vials
3 sterile silicone-free syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution and dilution
Read the package leaflet before reconstitution and use.
For single use only.
Use the silicone-free disposable syringe included in the package for reconstitution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Read the package leaflet for the shelf-life of the reconstituted product.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard any unused solution.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/000/000

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

TRAY LABEL

1. NAME OF THE MEDICINAL PRODUCT

ORENCIA 250 mg powder for concentrate for solution for infusion
Abatacept

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Use the silicone-free disposable syringe included in the package for reconstitution.
Store in a refrigerator.
Store in the original package in order to protect from light.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ORENCIA 250 mg powder for concentrate for solution for infusion
Abatacept
Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

250 mg of abatacept

6. OTHER

Use the silicone-free disposable syringe included in the package for reconstitution.

Bristol-Myers Squibb Pharma EEIG

PATIENT ALERT CARD TEXT

Orencia Patient Alert Card This alert card contains important safety information that you need to be aware of before you are given ORENCIA and during treatment with ORENCIA. • Show this card to any doctor involved in your treatment. **Infections** ORENCIA increases the risk of getting infections. - You should not be treated with ORENCIA if you have severe infection. - You should be screened for certain infections prior to treatment with ORENCIA, according to relevant guidelines. **Tuberculosis (TB)**: The safety of ORENCIA in individuals with latent TB is unknown. You should be screened for TB prior to ORENCIA treatment. It is very important that you tell your doctor if you have ever had TB, or if you have been in close contact with someone who has had TB. **Hepatitis**: Anti-rheumatic therapies have been associated with hepatitis B reactivation. You should be screened for viral hepatitis in accordance with published guidelines.	**Infections** – If you develop symptoms suggestive of infections, such as fever, persistent cough, weight loss, or listlessness, seek medical attention immediately. **Dates of ORENCIA Treatment**: Start: _____ Most recent: _____ • See the ORENCIA package leaflet for more information. • Please make sure you also have a list of all your other medicines with you at any visit to a health care professional. Patient's Name: _____ Doctor's Name: _____ Doctor's Phone: _____ Keep this card with you for 3 months after the last ORENCIA dose, since side effects may occur a long time after your last dose of ORENCIA.

B. PACKAGE LEAFLET

PACKAGE LEAFLET: **INFORMATION FOR THE USER**
ORENCIA 250 mg powder for concentrate for solution for infusion
Abatacept

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT ORENCIA IS AND WHAT IT IS USED FOR

ORENCIA is an infusion treatment for adults with moderate to severe rheumatoid arthritis and is used in combination with a medicine called methotrexate. The active ingredient of ORENCIA, abatacept, is a protein produced in cell cultures.

Rheumatoid arthritis is a long-term progressive systemic disease that, if untreated, can lead to serious consequences, such as joint destruction, increased disability and impairment of daily activities. In people with rheumatoid arthritis the body's own immune system attacks normal body tissues, leading to pain and swelling of the joints. This can cause joint damage. ORENCIA lessens the immune system's attack on normal tissues by interfering with the immune cells (called T lymphocytes) that contribute to the development of rheumatoid arthritis.

ORENCIA is used after another group of medicines called TNF blockers. ORENCIA is used to:
- slow down the damage to your joints
- improve your physical function

2. BEFORE YOU USE ORENCIA

Do not use ORENCIA
- **If you are allergic** (hypersensitive) to abatacept or any of the other ingredients.
- **If you have a severe or uncontrolled infection**, therapy with ORENCIA must not be started. Having an infection could put you at risk of serious side effects from ORENCIA.

Take special care with ORENCIA
- **If you experience allergic reactions** such as chest tightness, wheezing, severe dizziness or lightheadedness, swelling or skin rash **tell your doctor immediately**.
- **If you have any kind of infection**, including long-term or localised infection, or often get infections. **It is important you tell your doctor if you have symptoms of infection (e.g. fever, malaise, dental problems).** ORENCIA also can lower your body's ability to fight infection and the treatment can make you more prone to getting infections or make any infection you have worse.
- **If you have had tuberculosis (TB)** or have symptoms of tuberculosis (persistent cough, weight loss, listlessness, mild fever) **tell your doctor**. Before you use ORENCIA, your doctor will examine you for tuberculosis or do a skin test.

- **If you have viral hepatitis** tell your doctor. Before you use ORENCIA, your doctor may examine you for hepatitis.
- **If you have cancer**. Your doctor will have to decide if you can still be given ORENCIA.
- **If you recently had a vaccination** or are planning to have one. Some vaccines should not be given while receiving ORENCIA. **Check with your doctor before you receive any vaccines.**
- **If you are using a blood glucose monitor** to check your blood glucose levels. ORENCIA contains maltose, which is a type of sugar that can give falsely high blood glucose readings with certain types of blood glucose monitors. Your doctor may recommend a different method for monitoring your blood glucose levels.

ORENCIA and older people
ORENCIA can be used by people over 65 with no change in dose. Since the elderly are more susceptible to infections and cancer, ORENCIA should be used with caution in this patient population.

ORENCIA and children / adolescents
ORENCIA has not been studied in patients under 18 years of age, therefore ORENCIA is not recommended in this patient population.

Using other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
ORENCIA is not to be used with biological medicines for rheumatoid arthritis including adalimumab, etanercept, and infliximab; there is insufficient evidence to recommend co-administration with anakinra and rituximab.
ORENCIA can be taken with other medicines commonly used in the treatment of rheumatoid arthritis, such as steroids or painkillers including non-steroidal anti-inflammatories such as ibuprofen or diclofenac.
Ask your doctor or pharmacist for advice before taking any other medicine while using ORENCIA.

Pregnancy and breast-feeding
The effects of ORENCIA in pregnancy are not known, so do not use ORENCIA if you are pregnant unless your doctor specifically recommends it. Pregnancy must be avoided while using ORENCIA. Your doctor will advise you on adequate contraceptive methods while using ORENCIA and up to 14 weeks after the last dose. If you become pregnant while using ORENCIA, tell your doctor.

It is not known whether abatacept, the active ingredient, passes into human milk. Y**ou must stop breast-feeding** if you are being treated with ORENCIA and for up to 14 weeks after the last dose.

Driving and using machines
If you are feeling tired or unwell after receiving ORENCIA, you should not drive or operate any machinery. It is not known if ORENCIA will affect the ability to drive or use machines.

Important information about some of the ingredients of ORENCIA
This medicine contains 1.5 mmol (or 34.5 mg) sodium per maximum dose of 4 vials (0.375 mmol or 8.625 mg sodium per vial). To be taken into consideration by patients on a controlled sodium diet.

3. HOW TO USE ORENCIA

ORENCIA is supplied as a powder for solution for infusion. This means that before ORENCIA is given to you, it is first dissolved in water for injections, then further diluted with sodium chloride 9 mg/ml (0.9%) solution for injection.

The recommended dose of abatacept given to you is based on your body weight:

Your weight	Dose	Vials
Less than 60 kg	500 mg	2
60 kg - 100 kg	750 mg	3
More than 100 kg	1000 mg	4

How ORENCIA is given to you
ORENCIA is given to you into a vein, usually in your arm, over a period of 30 minutes. This procedure is referred to as an infusion. Healthcare professionals will monitor you while you receive your ORENCIA infusion.

How often ORENCIA is given to you
ORENCIA should be given to you again, 2 and then 4 weeks after the first infusion. After that you will receive a dose every 4 weeks. Your doctor will advise you on the duration of treatment and what other medications you may continue to take while on ORENCIA.

If you use more ORENCIA than you should
In case this happens, your doctor will monitor you for any signs or symptoms of side effects, and treat these symptoms if necessary.

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

If you stop using ORENCIA
The decision to stop using ORENCIA should be discussed with your doctor.

If you have any further questions on the use of this product, **ask your doctor or pharmacist**.

4. POSSIBLE SIDE EFFECTS

Like all medicines, ORENCIA can cause side effects, although not everybody gets them. The most common side effects with ORENCIA are headache and nausea. Like all medicines that affect your immune system, ORENCIA can cause serious side effects, which may need treatment.

Possible serious side effects include serious infections, malignancies and allergic reactions.

Tell your doctor immediately if you notice any of the following:
- Severe rash, hives or other signs of allergic reaction
- Swollen face, hands, feet
- Trouble breathing or swallowing

Tell your doctor as soon as possible if you notice any of the following:
- Signs of infection such as fever, malaise, dental problems, burning sensation during urination, painful skin rash, painful skin blisters, coughing

The symptoms described above can be signs of the side effects listed below, all of which have been observed with ORENCIA in clinical trials:

Very common side effects (at least 1 in 10 patients): headache.

Common side effect (at least 1 in 100 and less than 1 in 10 patients): infections of nose, throat and lungs, urinary infections, painful skin blisters (herpes), rhinitis, dizziness, high blood pressure, flushing, cough, nausea, diarrhoea, upset stomach, abdominal pain, rash, fatigue, weakness and abnormal liver function tests.

Uncommon side effects (at least 1 in 1,000 and less than 1 in 100 patients): tooth infection, infected skin ulcer, nail fungal infection, skin cancer, low blood platelet count, low blood cell counts, allergic reactions, anxiety, numbness, hives, eye inflammation, dry eye, reduced vision, palpitation, rapid heart rate, low heart rate, low blood pressure, hot flush, mouth sores, increased tendency to bruise, hair loss, dry skin, painful joints, pain in the extremities, flu-like illness, increased weight, infusion-related reactions, depression, absence of menstruation, migraine, kidney infection, psoriasis, difficulty in breathing and throat tightness.

Rare side effects (at least 1 in 10,000 and less than 1 in 1,000 patients): blood stream infection.

Your doctor may also do tests to examine your blood values.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ORENCIA

Keep out of the reach and sight of children.

Do not use after the expiry date which is stated on the label and the carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C).

Store in the original package in order to protect from light.

After reconstitution and dilution, the infusion solution is stable for 24 hours in a refrigerator, but for bacteriological reasons, it is to be used immediately.

Do not use ORENCIA if you notice opaque particles, discolouration or other foreign particles present in the infusion solution.

6. FURTHER INFORMATION

What ORENCIA contains
- The active substance is abatacept.
- Each vial contains 250 mg of abatacept.
- After reconstitution, each ml contains 25 mg of abatacept.

- The other ingredients are maltose, sodium dihydrogen phosphate monohydrate and sodium chloride.

What ORENCIA looks like and contents of the pack
ORENCIA powder for concentrate for solution for infusion is a white to off-white powder that can appear solid or broken into pieces.
ORENCIA is available in packs of either 1, 2 or 3 vials and is supplied with respectively 1, 2 or 3 silicone-free syringes.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder:
Bristol-Myers Squibb Pharma EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

Manufacturer:
Bristol-Myers Squibb S.R.L.
Contrada Fontana del Ceraso
I-03012 Anagni-Frosinone
Italy

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved in (MM/YYYY)

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/

The following information is intended for medical or healthcare professionals only

Reconstitution and dilution should be performed in accordance with good practices rules, particularly with respect to asepsis.

Dose selection: see section 3 'How to use ORENCIA' of the Package Leaflet

Reconstitution of vials: under aseptic conditions, reconstitute each vial with 10 ml of water for injections, using the **silicone-free disposable syringe provided with each vial** and an 18-21 gauge needle. Remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the centre of the rubber stopper and direct the stream of water for injections to the glass wall of the vial. Do not use the vial if a vacuum is not present. Remove the syringe and needle after 10 ml of water for injections have been injected into the vial. To minimise foam formation in solutions of ORENCIA the vial should be rotated with gentle swirling until the contents are completely dissolved. **Do not shake**. **Do not use prolonged or vigorous agitation**. Upon complete dissolution of the powder, the vial should be vented with a needle to dissipate any foam that may be present. After reconstitution the solution should be clear and colourless to pale yellow. Do not use if opaque particles, discolouration, or other foreign particles are present.

Preparation of infusion: immediately after reconstitution, dilute the product to 100 ml with sodium chloride 9 mg/ml (0.9%) solution for injection. From a 100 ml infusion bag or bottle, withdraw a volume of 0.9% sodium chloride injection 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 to 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 abatacept are used.

Administration: when reconstitution and dilution are performed under aseptic conditions ORENCIA infusion solution can be used immediately or within 24 hours if stored refrigerated at 2°C to 8°C. However, for microbiological reasons, it is to be used immediately. Prior to administration, the ORENCIA solution should be inspected visually for particulate matter and discolouration. Discard the solution if any particulate matter or discolouration is observed. 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). Do not store any unused portion of the infusion solution for reuse.

Other medicines: ORENCIA should not be mixed with other medicines or infused concomitantly in the same intravenous line with other medicines. No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of ORENCIA with other agents.

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