SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

ORENCIA 87.5 mg solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ORENCIA 87.5 mg solution for injection in pre-filled syringe

Each pre-filled syringe contains 87.5 mg of abatacept in 0.7 mL.

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

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection).

The solution is clear, colourless to pale yellow with a pH of 6.8 to 7.4.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

ORENCIA, in combination with methotrexate, is indicated for:

the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who responded inadequately to previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate (MTX) or a tumour necrosis factor (TNF)-alpha inhibitor.

the treatment of highly active and progressive disease in adult patients with rheumatoid arthritis not previously treated with methotrexate.

A reduction in the progression of joint damage and improvement of physical function have been demonstrated during combination treatment with abatacept and methotrexate.

Psoriatic arthritis

ORENCIA, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients when the response to previous DMARD therapy including MTX has been inadequate, and for whom additional systemic therapy for psoriatic skin lesions is not required.

Polyarticular juvenile idiopathic arthritis

ORENCIA in combination with methotrexate is indicated for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis (pJIA) in paediatric patients 2 years of age and older who have had an inadequate response to previous DMARD therapy.

ORENCIA can be given as monotherapy in case of intolerance to methotrexate or when treatment with methotrexate is inappropriate.

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.

If a response to abatacept is not present within 6 months of treatment, the continuation of the treatment should be reconsidered (see section 5.1).

Posology

Rheumatoid arthritis

Adults

ORENCIA subcutaneous (SC) may be initiated with or without an intravenous (IV) loading dose. ORENCIA SC should be administered weekly at a dose of 125 mg abatacept by subcutaneous injection regardless of weight (see section 5.1). If a single IV infusion is given to initiate treatment (IV loading dose before SC administration), the first 125 mg abatacept SC should be administered within a day of the IV infusion, followed by the weekly 125 mg abatacept SC injections (for the posology of the intravenous loading dose, please refer to section 4.2 of ORENCIA 250 mg powder for concentrate for solution for infusion).

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

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

Psoriatic arthritis

Adults

ORENCIA should be administered weekly at a dose of 125 mg by subcutaneous (SC) injection without the need for an intravenous (IV) loading dose.

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

Paediatric population

Polyarticular juvenile idiopathic arthritis

The recommended weekly dose of ORENCIA solution for injection in pre-filled syringe for patients 2 to 17 years of age with polyarticular juvenile idiopathic arthritis should be initiated without an intravenous loading dose and administered utilizing the weight range-based dosing as specified in the table below:

Table 1: Weekly dose of ORENCIA

Body weight of patient	**Dose**

10 kg to less than 25 kg	50 mg
25 kg to less than 50 kg	87.5 mg
50 kg or more	125 mg

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

ORENCIA powder for concentrate for solution for infusion for intravenous administration is available for paediatric patients 6 years of age and older for the treatment of pJIA (see Summary of Product Characteristics for ORENCIA powder for concentrate for solution for infusion).

Missed dose

If a patient misses an injection of abatacept and is within three days of the planned date, he/she should be instructed to take the missed dose immediately and remain on the original weekly schedule. If the dose is missed by more than three days, the patient should be instructed when to take the next dose based on medical judgment (condition of the patient, status of disease activity, etc).

Special populations

Elderly patients

No dose adjustment is required (see section 4.4).

Renal and hepatic impairment

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

Paediatric population

The safety and efficacy of ORENCIA in children below 2 years of age have not been established. No data are available.

There is no relevant use of ORENCIA in children under two years old.

Method of administration

For subcutaneous use.

ORENCIA is intended for use under the guidance of a healthcare professional. After proper training in subcutaneous injection technique, a patient or caregiver may inject

with ORENCIA if a physician/healthcare professional determines that it is appropriate.

The total content of the pre-filled syringe should be administered as a subcutaneous injection only. Injection sites should be rotated and injections should never be given into areas where the skin is tender, bruised, red, or hard.

Comprehensive instructions for the preparation and administration of ORENCIA in a pre-filled syringe are given in the package leaflet and “Important instructions for use”.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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-inhibitors

There is limited experience with use of abatacept in combination with TNF-inhibitors (see section 5.1). In placebo-controlled clinical trials, in comparison with patients treated with TNF-inhibitors and placebo, patients who received combination TNF-inhibitors 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-inhibitors.

While transitioning from TNF-inhibitor therapy to ORENCIA therapy, patients should be monitored for signs of infection (see section 5.1, study VII).

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). Anaphylaxis or anaphylactoid reactions can occur after the first infusion and can be life-threatening. In postmarketing experience, a case of fatal anaphylaxis following the first infusion of ORENCIA has been reported. If any serious allergic or anaphylactic reaction occurs, intravenous or subcutaneous ORENCIA therapy should be discontinued immediately and appropriate therapy initiated, and the use of ORENCIA should be permanently discontinued (see section 4.8).

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 abatacept on the immune system (see section 4.5).

Infections
Serious infections, including sepsis and pneumonia, have been reported with abatacept (see section 4.8). Some of these infections have been fatal. Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy which in addition to their underlying disease, could further predispose them to infections. 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; however, all ORENCIA patients were screened for tuberculosis. The safety of ORENCIA in individuals with latent tuberculosis is unknown. There have been reports of tuberculosis in patients receiving ORENCIA (see section 4.8). 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.

Progressive multifocal leukoencephalopathy (PML)
Cases of PML have been reported in patients receiving abatacept mostly in combination with other immunosuppressive medication. PML can be fatal and should be considered in the differential diagnosis in immunosuppressed patients with new onset or worsening neurological, psychiatric and cognitive symptoms. If symptoms suggestive of PML occur during ORENCIA therapy, treatment with ORENCIA should be discontinued and appropriate diagnostic measures initiated.

Malignancies
In the placebo-controlled clinical trials, the frequencies of malignancies in abatacept- and placebo-treated patients were 1.2% and 0.9%, respectively (see section 4.8). Patients with known malignancies were not included in these clinical trials. In carcinogenicity studies in mice, an increase in lymphomas and mammary tumours were noted. The clinical significance of this observation is unknown (see section 5.3). The potential role of abatacept in the development of malignancies, including lymphoma, in humans is unknown. There have been reports of non-melanoma skin cancers in patients receiving ORENCIA (see section 4.8). Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Vaccinations
Patients treated with ORENCIA may receive concurrent vaccinations, except for live vaccines. Live vaccines should not be given concurrently with abatacept or within 3 months of its discontinuation. Medicinal products that affect the immune system, including abatacept, may blunt the effectiveness of some immunisations (see section 4.5).

Elderly patients

A total of 404 patients 65 years of age and older, including 67 patients 75 years and older, received intravenous abatacept in placebo-controlled clinical trials. A total of 270 patients 65 years of age and older, including 46 patients 75 years and older, received subcutaneous abatacept in controlled clinical trials. The frequencies of serious infection and malignancy relative to placebo among intravenous abatacept-treated patients over age 65 were higher than among those under age 65. Similarly, the frequencies of serious infection and malignancy among subcutaneous 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 abatacept might increase the risk for autoimmune processes in adults, 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 sections 4.8 and 5.3).

Patients on controlled sodium diet

This medicinal product contains less than 1 mmol sodium (23 mg) per pre-filled syringe, that is to say essentially ‘sodium-free’.

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

4.5 Interaction with other medicinal products and other forms of interaction

Combination with TNF-inhibitors

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

Combination with other medicinal products that affect the immune system and with vaccinations

Co-administration of abatacept with biologic immunosuppressive or immunomodulatory agents could potentiate the effects of abatacept on the immune system. There is insufficient evidence to assess the safety and efficacy of abatacept in combination with anakinra or rituximab (see section 4.4).

Vaccinations

Live vaccines should not be given concurrently with abatacept 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 abatacept. Medicinal products that affect the immune system, including abatacept, may blunt the effectiveness of some immunisations (see sections 4.4 and 4.6).

Exploratory studies to assess the effect of abatacept on the antibody response to vaccination in healthy subjects as well as the antibody response to influenza and pneumococcal vaccines in rheumatoid arthritis patients suggested that abatacept may blunt the effectiveness of the immune response, but did not significantly inhibit the ability to develop a clinically significant or positive immune response.

Abatacept was evaluated in an open-label study in rheumatoid arthritis patients administered the 23-valent pneumococcal vaccine. After pneumococcal vaccination, 62 of 112 abatacept-treated patients were able to mount an adequate immune response of at least a 2-fold increase in antibody titers to pneumococcal polysaccharide vaccine.

Abatacept was also evaluated in an open-label study in rheumatoid arthritis patients administered the seasonal influenza trivalent virus vaccine. After influenza vaccination, 73 of 119 abatacept-treated patients without protective antibody levels at baseline were able to mount an adequate immune response of at least a 4-fold increase in antibody titers to trivalent influenza vaccine.

4.6 Fertility, pregnancy and lactation

Pregnancy and women of childbearing potential

There are no adequate data from use of abatacept in pregnant women. In pre-clinical embryo-fetal 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 in rats, limited changes in immune function were observed at 11-fold higher than a human 10 mg/kg dose based on AUC (see section 5.3).

ORENCIA should not be used during pregnancy unless the clinical condition of the woman requires treatment with abatacept.

Women of childbearing potential have to use effective contraception during treatment and up to 14 weeks after the last dose of abatacept.

Abatacept may cross the placenta into the serum of infants born to women treated with abatacept during pregnancy. Consequently, these infants may be at increased risk of infection. The safety of administering live vaccines to infants exposed to abatacept *in utero* is unknown. Administration of live vaccines to infants exposed to abatacept *in utero* is not recommended for 14 weeks following the mother's last exposure to abatacept during pregnancy.

Breast-feeding

Abatacept has been shown to be present in rat milk.

It is unknown whether abatacept is excreted in human milk.

A risk to the newborns/infants cannot be excluded.

Breast-feeding should be discontinued during treatment with ORENCIA and for up to 14 weeks after the last dose of abatacept treatment.

Fertility

Formal studies of the potential effect of abatacept 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

Based on its mechanism of action, abatacept is expected to have no or negligible influence on the ability to drive and use machines. However, dizziness and reduced visual acuity have been reported as common and uncommon adverse reactions respectively from patients treated with ORENCIA, therefore if a patient experiences such symptoms, driving and use of machinery should be avoided.

4.8 Undesirable effects

Summary of the safety profile in rheumatoid arthritis

Abatacept has been studied in patients with active rheumatoid arthritis in placebo-controlled clinical trials (2,653 patients with abatacept, 1,485 with placebo).
In placebo-controlled clinical trials with abatacept, adverse reactions (ARs) were reported in 49.4% of abatacept-treated patients and 45.8% of placebo-treated patients. The most frequently reported adverse reactions (≥ 5%) among abatacept-treated patients were headache, nausea, and upper respiratory tract infections (including sinusitis). The proportion of patients who discontinued treatment due to ARs was 3.0% for abatacept-treated patients and 2.0% for placebo-treated patients.

Tabulated list of adverse reactions

Listed in Table 2 are adverse reactions observed in clinical trials and post-marketing experience 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: Adverse reactions

Infections and infestations	Very Common	Upper respiratory tract infection (including tracheitis, nasopharyngitis, and sinusitis)
	Common	Lower respiratory tract infection (including bronchitis), urinary tract infection, herpes infections (including herpes simplex, oral herpes, and herpes zoster), pneumonia, influenza
	Uncommon	Tooth infection, onychomycosis, sepsis, muskuloskeletal infections, skin abscess, pyelonephritis, rhinitis, ear infection
	Rare	Tuberculosis, bacteraemia, gastrointestinal infection, pelvic inflammatory disease
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Uncommon	Basal cell carcinoma, skin papilloma
	Rare	Lymphoma, lung neoplasm malignant, squamous cell carcinoma
Blood and lymphatic system disorders	Uncommon	Thrombocytopenia, leukopenia
Immune system disorders	Uncommon	Hypersensitivity
Psychiatric disorders	Uncommon	Depression, anxiety, sleep disorder (including insomnia)
Nervous system disorders	Common	Headache, dizziness
	Uncommon	Migraine, paraesthesia

Eye disorders	Uncommon	Conjunctivitis, dry eye, visual acuity reduced
Ear and labyrinth disorders	Uncommon	Vertigo
Cardiac disorders	Uncommon	Palpitations, tachycardia, bradycardia
Vascular disorders	Common Uncommon	Hypertension, blood pressure increased Hypotension, hot flush, flushing, vasculitis, blood pressure decreased
Respiratory, thoracic and mediastinal disorders	Common Uncommon	Cough Chronic obstructive pulmonary disease exacerbated, bronchospasm, wheezing, dyspnea, throat tightness
Gastrointestinal disorders	Common Uncommon	Abdominal pain, diarrhoea, nausea, dyspepsia, mouth ulceration, aphthous stomatitis, vomiting Gastritis
Hepatobiliary disorders	Common	Liver function test abnormal (including transaminases increased)
Skin and subcutaneous tissue disorders	Common Uncommon	Rash (including dermatitis) Increased tendency to bruise, dry skin, alopecia, pruritus, urticaria, psoriasis, acne, erythema, hyperhidrosis
Musculoskeletal and connective tissue disorders	Uncommon	Arthralgia, pain in extremity
Reproductive system and breast disorders	Uncommon	Amenorrhea, menorrhagia
General disorders and administration site conditions	Common Uncommon	Fatigue, asthenia, local injection site reactions, systemic injection reactions* Influenza like illness, weight increased

*(e.g. pruritus, throat tightness, dyspnea)

Description of selected adverse reactions

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

Serious infections at least possibly related to treatment were reported in 1.5% of abatacept-treated patients and 1.1% of placebo-treated patients. The type of serious infections was similar between the abatacept and placebo treatment groups (see section 4.4).

The incidence rates (95% CI) for serious infections was 3.0 (2.3, 3.8) per 100 patient-years for abatacept-treated patients and 2.3 (1.5, 3.3) per 100 patient-years for placebo-treated patients in the double-blind studies.

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

Malignancies
In placebo-controlled clinical trials, malignancies were reported in 1.2% (31/2,653) of abatacept-treated patients, and in 0.9% (14/1,485) of placebo-treated patients. The incidence rates for malignancies was 1.3 (0.9, 1.9) per 100 patient-years for abatacept-treated patients and 1.1 (0.6, 1.9) per 100 patient-years for placebo-treated patients.

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

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

The most frequently reported organ cancer in the placebo-controlled clinical trials was lung cancer 0.17 (0.05, 0.43) per 100 patient-years for abatacept-treated patients, 0 for placebo-treated patients and 0.12 (0.08, 0.17) per 100 patient-years in the cumulative period. The most common hematologic malignancy was lymphoma 0.04 (0, 0.24) per 100 patient-years for abatacept-treated patients, 0 for placebo-treated patients, and 0.06 (0.03, 0.1) per 100 patient-years in the cumulative period.

Adverse reactions in patients with chronic obstructive pulmonary disease (COPD)
In study IV, there were 37 patients with COPD treated with intravenous abatacept and 17 treated with placebo. The COPD patients treated with abatacept developed adverse 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%]).

Autoimmune processes
Abatacept therapy did not lead to increased formation of autoantibodies, i.e., antinuclear and anti-dsDNA antibodies, compared with placebo.

The incidence rate of autoimmune disorders in abatacept-treated patients during the double-blind period was 8.8 (7.6, 10.1) per 100 person-years of exposure and for placebo-treated patients was 9.6 (7.9, 11.5) per 100 person-years of exposure. The incidence rate in abatacept-treated patients was 3.8 per 100 person-years in the cumulative period. The most frequently reported autoimmune-related disorders other than the indication being studied during the cumulative period were psoriasis, rheumatoid nodule, and Sjogren's syndrome.

Immunogenicity in adults treated with intravenous abatacept
Antibodies directed against the abatacept molecule were assessed by ELISA assays in 3,985 rheumatoid arthritis patients treated for up to 8 years with abatacept. One hundred and eighty-seven of 3,877 (4.8%) patients developed anti-abatacept antibodies while on treatment. In patients assessed for anti-abatacept antibodies after discontinuation of abatacept (> 42 days after last dose), 103 of 1,888 (5.5%) were seropositive.

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

Overall, there was no apparent correlation of antibody development to clinical response or adverse events. However, the number of patients that developed antibodies was too limited to make a definitive assessment. Because immunogenicity analyses are product-specific, comparison of antibody rates with those from other products is not appropriate.

Immunogenicity in adults treated with subcutaneous abatacept
Study SC-I compared the immunogenicity to abatacept following subcutaneous or intravenous administration as assessed by ELISA assay. During the initial double blind 6 months period (short-term period), the overall immunogenicity frequency to abatacept was 1.1% (8/725) and 2.3% (16/710) for the subcutaneous and intravenous groups, respectively. The rate is consistent with previous experience, and there was no effect of immunogenicity on pharmacokinetics, safety, or efficacy.

Immunogenicity to abatacept following long-term subcutaneous administration was assessed by a new electrochemiluminescence (ECL) assay. Comparison of incidence rates across different assays is not appropriate, as the ECL assay was developed to be more sensitive and drug tolerant than the previous ELISA assay. The cumulative immunogenicity frequency to abatacept by the ECL assay with at least one positive sample in the short-term and long-term periods combined was 15.7% (215/1369) while on abatacept, with a mean duration of exposure of 48.8 months, and 17.3% (194/1121) after discontinuation (> 21 days up to 168 days after last dose). The exposure adjusted incidence rate (expressed per 100 person-years) remained stable over the treatment duration.

Consistent with previous experience, titers and persistence of antibody responses were generally low and did not increase upon continued dosing (6.8% subjects were seropositive on 2 consecutive visits), and there was no apparent correlation of antibody development to clinical response, adverse events, or pharmacokinetics.

In study SC-III, similar immunogenicity rates were seen in patients on treatment for the abatacept+MTX, and abatacept monotherapy groups (2.9% (3/103) and 5.0% (5/101), respectively) during the double-blind 12 month period. As in study SC-I, there was no effect of immunogenicity on safety or efficacy.

Immunogenicity and safety of abatacept upon withdrawal and restart of treatment
A study in the subcutaneous program was conducted to investigate the effect of withdrawal (three months) and restart of abatacept subcutaneous treatment on immunogenicity. Upon withdrawal of abatacept subcutaneous treatment, the increased rate of immunogenicity was consistent with that seen upon discontinuation of abatacept administered intravenously. Upon reinitiating therapy, there were no injection reactions and no other safety concerns in patients who were withdrawn from subcutaneous therapy for up to 3 months relative to those who remained on subcutaneous therapy, whether therapy was reintroduced with or without an intravenous loading dose. The safety observed in the treatment arm that reinitiated therapy

without an intravenous loading dose was also consistent with that observed in the other studies.

In SC-III, increased rates of immunogenicity were observed in subjects tested during 6 months of complete drug withdrawal in the abatacept+MTX and abatacept monotherapy groups (37.7% [29/77] and 44.1% [27/59], respectively) with generally low titer antibody responses. No clinical impact of these antibody responses was detected, and no safety concerns were observed upon reinitiation of abatacept therapy.

Injection Reactions in adult patients treated with subcutaneous abatacept
Study SC-I compared the safety of abatacept including injection site reactions following subcutaneous or intravenous administration. The overall frequency of injection site reactions was 2.6% (19/736) and 2.5% (18/721) for the subcutaneous abatacept group and the subcutaneous placebo group (intravenous abatacept), respectively. All injection site reactions were described as mild to moderate (hematoma, pruritus, or erythema) and generally did not necessitate drug discontinuation. During the cumulative study period when all subjects treated with abatacept in 7 SC studies were included, the frequency of injection site reactions was 4.6% (116/2,538) with an incidence rate of 1.32 per 100 person-years.
Postmarketing reports of systemic injection reactions (e.g. pruritus, throat tightness, dyspnea) have been received following the use of subcutaneous ORENCIA.

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 summarised in section 5.1.

Summary of the safety profile in psoriatic arthritis

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

Paediatric population

Abatacept has been studied in patients with pJIA in 2 clinical trials (ongoing pJIA SC study and pJIA IV study). The pJIA SC study included 46 patients in the 2 to 5 year age cohort and 173 patients in the 6 to 17 year age cohort. The pJIA IV study included 190 patients in the 6 to 17 year age cohort. During the first 4-month open-label period, the overall safety profile in these 409 pJIA patients was similar to that observed in the RA population with the following exceptions in the pJIA patients:

Common adverse reactions: pyrexia
Uncommon adverse reactions: haematuria, otitis (media and externa).

Description of selected adverse reactions

Infections
Infections were the most commonly reported adverse events in patients with pJIA. The types of infections were consistent with those commonly seen in outpatient paediatric populations. During the first 4-month treatment period of intravenous and subcutaneous abatacept in 409 patients with pJIA, the most common adverse reactions were nasopharyngitis (3.7% patients)

and upper respiratory tract infection (2.9% patients). Two serious infections (varicella and sepsis) were reported during the initial 4 months of treatment with abatacept.

Injection reactions
Of the 219 patients with pJIA treated with subcutaneous abatacept during the first 4-month abatacept treatment, the frequency of local injection reactions was 4.6% (10/219); injection site pain and injection site erythema were the most frequently reported local injection reactions. No systemic hypersensitivity reactions were reported.

Immunogenicity in patients with pJIA treated with subcutaneous abatacept
Antibodies directed against the whole abatacept molecule or to the CTLA-4 portion of abatacept were assessed by an ECL assay in patients with pJIA following repeated treatment with subcutaneous abatacept. Overall, 6.9% (15/218) of subjects (cohorts combined) had a positive immunogenicity response relative to baseline during the cumulative period, including the 4-month short-term treatment period, 20-month extension treatment period and the 6-month post abatacept follow-up period. In the 6 to 17 year age cohort, the overall rate of seropositivity during the cumulative period including post abatacept follow-up was 4.7% (8/172): 2.3% (4/172) on treatment and 13.6% (6/44) after discontinuation of abatacept (≥ 28 days after the last dose). In the 2 to 5 year age cohort, the overall rate of seropositivity during the cumulative period including post abatacept follow-up was 15.2% (7/46): 10.9% (5/46) on treatment and 37.5% (3/8) after discontinuation of abatacept (≥ 28 days after the last dose).

Overall antibodies against abatacept were generally transient and of low titer. The absence of concomitant methotrexate did not appear to be associated with a higher rate of seropositivity. The significance of the higher incidence in the 2 to 5 year age cohort is unknown, taking into account the difference in sample size. The presence of antibodies was not associated with adverse reactions, or with changes in efficacy or serum abatacept concentrations, in either cohort.

Long-term extension period
During the extension period of the pJIA studies (20 months in the pJIA ongoing SC study and 5 years in the pJIA IV study), the safety profile in the pJIA patients aged 6 to 17 years was comparable to that seen in adult patients. One patient was diagnosed with multiple sclerosis while in the extension period of the pJIA IV study. One serious adverse reaction of infection (limb abscess) was reported in the 2 to 5 year age cohort during the 20-month extension period of the pJIA SC study.

Long-term safety data in 2 to 5 year age cohort with pJIA was limited, but the existing evidence did not reveal any new safety concern in this younger paediatric population. During the 24-month cumulative period of the pJIA SC study (4-month shortterm period plus 20-month extension period), a higher frequency of infections was reported in the 2 to 5 year age cohort (87.0%) compared to that reported in the 6 to 17 year age cohort (68.2%). This was mostly due to non-serious upper respiratory tract infections in the 2 to 5 year age cohort.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

United Kingdom
Yellow Card Scheme
Website: at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

Doses up to 50 mg/kg have been administered intravenously 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: Immunosuppressants, 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 in adult rheumatoid arthritis

The efficacy and safety of intravenous 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, V, and VI required patients to have at least 12 tender and 10 swollen joints at randomisation. Study IV did not require any specific number of tender or swollen joints. Study SC-I was a randomised, double-blind, double-dummy non-inferiority study administered to patients stratified by body weight (< 60 kg, 60 to 100 kg, > 100 kg) that compared the efficacy and safety of abatacept administered subcutaneously and intravenously in subjects with rheumatoid arthritis (RA), receiving background methotrexate (MTX), and experiencing an inadequate response to MTX (MTX-IR).

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-inhibitor, with the TNF-inhibitor discontinued prior to randomisation; 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. In study VI, the efficacy and safety of abatacept were assessed in methotrexate-naive, Rheumatoid Factor (RF) and/or anti-Cyclic Citrullinated Peptide 2 (Anti-CCP2)-positive patients with early, erosive rheumatoid arthritis (≤ 2 years disease duration) who were randomised to receive abatacept plus methotrexate or methotrexate plus placebo. In study SC-I, the goal was to demonstrate non-inferiority of the efficacy and comparability of the safety of abatacept subcutaneous relative to intravenous administration in subjects with moderate to severely active RA and experiencing inadequate response to MTX. Study SC-II investigated the relative efficacy and safety of abatacept and adalimumab, both given subcutaneously without an intravenous loading dose and with background MTX, in patients with moderate to severely active RA and an inadequate response to previous MTX therapy. In study SC-III, abatacept subcutaneous was evaluated in combination with methotrexate, or as abatacept monotherapy, and compared to MTX monotherapy in induction of remission following 12 months of treatment, and the possible maintenance of drug-free remission after complete drug withdrawal, in adult MTX-naive patients with highly active early rheumatoid arthritis (mean DAS28-CRP of 5.4; mean symptom duration less than 6.7 months) with poor prognostic factors for rapidly progressive disease (e.g. anti-citrullinated protein antibodies [ACPA+], as measured by anti-CCP2 assay, and/or RF+, baseline joint erosions).

Study I patients were randomised to receive abatacept 2 or 10 mg/kg or placebo for 12 months. Study II, III, IV, and VI patients were randomised to receive a fixed dose approximating 10 mg/kg of abatacept or placebo for 12 (studies II, IV, and VI) 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 1,000 mg for patients weighing greater than 100 kg. In study SC-I, abatacept was given subcutaneously to patients after a single loading dose of intravenous abatacept and then every week thereafter. Subjects continued taking their current dose of MTX from the day of randomisation. Study V patients were randomised 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, V, VI, SC-I, SC-II, and SC-III evaluated 339, 638, 389, 1441, 431, 509, 1371, 646, and 351 adult 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), study III (patients with inadequate response to TNF-inhibitor), study VI (methotrexate-naive patients), and study SC-I (subcutaneous abatacept) 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 VI, statistically significant improvement in the ACR 20 response in abatacept plus methotrexate-treated patients versus methotrexate plus placebo-treated patients was observed at 29 days, and was maintained through the duration of the study. 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.

In study SC-I, abatacept administered subcutaneously (SC) was non-inferior relative to intravenous IV infusions of abatacept with respect to ACR 20 responses up to 6 months of treatment. Patients treated with abatacept subcutaneously also achieved similar ACR 50 and 70 responses as those patients receiving abatacept intravenously at 6 months.
No difference in clinical response between subcutaneous and intravenous abatacept was seen across the 3 weight groups. In SC-I, the ACR 20 response rates at day 169 for subcutaneous and intravenous abatacept were respectively 78.3% (472/603 SC) and 76.0% (456/600 IV) in patients < 65 years, versus 61.1% (55/90 SC) and 74.4% (58/78 IV) for patients ≥ 65 years.

Table 3: Clinical responses in controlled trials

	Percent of patients							
	Intravenous administration						Subcutaneous administration	
	MTX-Naive		Inadequate response to MTX		Inadequate response to TNF Inhibitor		Inadequate response to MTX	
	Study VI		Study II		Study III		Study SC-I	
Response Rate	Abatacept[a] +MTX n = 256	Placebo +MTX n = 253	Abatacept[a] +MTX n = 424	Placebo +MTX n = 214	Abatacept[a] +DMARDs[b] n = 256	Placebo +DMARDs[b] n = 133	Abatacept[f] SC +MTX n=693	Abatacept[f] IV +MTX n=678
ACR 20								
Day 15	24%	18%	23%*	14%	18%**	5%	25%	25%
Month 3	64%[††]	53%	62%***	37%	46%***	18%	68%	69%
Month 6	75%[†]	62%	68%***	40%	50%***	20%	76%[§]	76%
Month 12	76%[‡]	62%	73%***	40%	NA[d]	NA[d]	NA	NA
ACR 50								
Month 3	40%[‡]	23%	32%***	8%	18%**	6%	33%	39%
Month 6	53%[‡]	38%	40%***	17%	20%***	4%	52%	50%
Month 12	57%[‡]	42%	48%***	18%	NA[d]	NA[d]	NA	NA
ACR 70								
Month 3	19%[†]	10%	13%***	3%	6%[††]	1%	13%	16%
Month 6	32%[†]	20%	20%***	7%	10%**	2%	26%	25%
Month 12	43%[‡]	27%	29%***	6%	NA[d]	NA[d]	NA	NA
Major Clinical Response[c]	27%[‡]	12%	14%***	2%	NA[d]	NA[d]	NA	NA
DAS28-CRP Remission[e]								
Month 6	28%[‡]	15%	NA	NA	NA	NA	24%[§§]	25%
Month 12	41%[‡]	23%	NA	NA	NA	NA	NA	NA

* $p < 0.05$, abatacept vs. placebo.
** $p < 0.01$, abatacept vs. placebo.
*** $p < 0.001$, abatacept vs. placebo.
[†] $p < 0.01$, abatacept plus MTX vs. MTX plus placebo
[‡] $p < 0.001$, abatacept plus MTX vs. MTX plus placebo
[††] $p < 0.05$, abatacept plus MTX vs. MTX plus placebo
[§] 95% CI: −4.2, 4.8 (based on prespecified margin for non-inferiority of −7.5%)
[§§]ITT data is presented in table
[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.
[e] DAS28-CRP Remission is defined as a DAS28-CRP score < 2.6
[f] Per protocol data is presented in table. For ITT; n=736, 721 for subcutaneous (SC) and intravenous (IV) abatacept, respectively

In the open-label extension of studies I, II, III, VI, and SC-I durable and sustained ACR 20, 50, and 70 responses have been observed through 7 years, 5 years, 5 years, 2 years, and 5 years, respectively, of abatacept treatment. In study I, ACR responses were assessed at

7 years in 43 patients with 72% ACR 20 responses, 58% ACR 50 responses, and 44% ACR 70 responses. In study II, ACR responses were assessed at 5 years in 270 patients with 84% ACR 20 responses, 61% ACR 50 responses, and 40% ACR 70 responses. In study III, ACR responses were assessed at 5 years in 91 patients with 74% ACR 20 responses, 51% ACR 50 responses, and 23% ACR 70 responses. In study VI, ACR responses were assessed at 2 years in 232 patients with 85% ACR 20 responses, 74% ACR 50 responses, and 54% ACR 70 responses. In study SC-I, ACR responses were assessed at 5 years with 85% (356/421) ACR 20 responses, 66% (277/423) ACR 50 responses, and 45% (191/425) ACR 70 responses.

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. There was a significant improvement of DAS in studies II, III, V, and VI as compared to placebo or comparator.

In study VI, which only included adults, a significantly higher proportion of patients in the abatacept plus methotrexate group (41%) achieved DAS28 (CRP)-defined remission (score < 2.6) versus the methotrexate plus placebo group (23%) at year 1. The response at year 1 in the abatacept group was maintained through year 2.

Study V: abatacept or infliximab versus placebo
A randomised, double-blind study was conducted to assess the safety and efficacy of intravenous 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. The open label period of the study provided an assessment of the ability of abatacept to maintain efficacy for subjects originally randomised to abatacept and the efficacy response of those subjects who were switched to abatacept following treatment with infliximab. The reduction from baseline in mean DAS28 score at day 365 (-3.06) was maintained through day 729 (-3.34) in those patients who continued with abatacept. In those patients who initially received infliximab and then switched to abatacept, the reduction in the mean DAS28 score from baseline were 3.29 at day 729 and 2.48 at day 365.

Study SC-II: abatacept versus adalimumab
A randomised, single(investigator)-blinded, non-inferiority study was conducted to assess the safety and efficacy of weekly subcutaneous (SC) abatacept without an abatacept intravenous (IV) loading dose versus every-other-weekly subcutaneous adalimumab, both with background MTX, in patients with an inadequate response to methotrexate (study SC-II). The primary endpoint showed non-inferiority (predefined margin of 12%) of ACR20 response after 12 months of treatment, 64.8% (206/318) for the abatacept SC group and 63.4% (208/328) for the adalimumab SC group; treatment difference was 1.8% [95% confidence interval (CI): -5.6, 9.2], with comparable responses throughout the 24-month period. The

respective values for ACR 20 at 24 months were 59.7% (190/318) for the abatacept SC group and 60.1% (197/328) for the adalimumab SC group. The respective values for ACR 50 and ACR 70 at 12 months and 24 months were consistent and similar for abatacept and adalimumab. The adjusted mean changes (standard error; SE) from baseline in DAS28-CRP were -2.35 (SE 0.08) [95% CI: -2.51, -2.19] and -2.33 (SE 0.08) [95% CI: -2.50, -2.17] in the SC abatacept group and the adalimumab group, respectively, at 24 months, with similar changes over time. At 24 months, 50.6% (127/251) [95% CI: 44.4, 56.8] of patients in abatacept and 53.3% (130/244) [95% CI: 47.0, 59.5] of patients in adalimumab groups achieved DAS 28 < 2.6. Improvement from baseline as measured by HAQ-DI at 24 months and over time was also similar between abatacept SC and adalimumab SC.

Safety and structural damage assessments were conducted at one and two years. The overall safety profile with respect to adverse reactions was similar between the two groups over the 24-month period. After 24 months, adverse reactions were reported in 41.5% (132/318) and 50% (164/328) of abatacept and adalimumab-treated patients. Serious adverse reactions were reported in 3.5% (11/318) and 6.1% (20/328) of the respective group. At 24 months, 20.8 % (66/318) of patients on abatacept and 25.3 % (83/328) on adalimumab had discontinued.
In SC-II, serious infections were reported in 3.8 % (12/318) of patients treated with abatacept SC weekly, none of which led to discontinuation and in 5.8 % (19/328) of patients treated with adalimumab SC every-other-week, leading to 9 discontinuations in the 24-month period. The frequency of local injection site reactions was 3.8% (12/318) and 9.1% (30/328) at 12 months (p=0.006) and 4.1% (13/318) and 10.4% (34/328) at 24 months for abatacept SC and adalimumab SC, respectively. Over the 2 year study period, 3.8 % (12/318) and 1.5 % (5/328) patients treated with abatacept SC and adalimumab SC respectively reported autoimmune disorders mild to moderate in severity (e.g., psoriasis, Raynaud's phenomenon, erythema nodosum).

Study SC-III: Induction of remission in methotrexate-naive RA patients
A randomised and double-blinded study evaluated abatacept SC in combination with methotrexate (abatacept + MTX), abatacept SC monotherapy, or methotrexate monotherapy (MTX group) in induction of remission following 12 months of treatment, and maintenance of drug-free remission after complete drug withdrawal in MTX-naive adult patients with highly active early rheumatoid arthritis with poor prognostic factors. Complete drug withdrawal led to loss of remission (return to disease activity) in all three treatment arms (abatacept with methotrexate, abatacept or methotrexate alone) in a majority of patients (Table 4).

Table 4: Remission rates at end of drug treatment and drug withdrawal phases in study SC-III

Number of patients	Abatacept SC+ MTX n = 119	MTX n = 116	Abatacept SC n = 116
Proportion of randomised patients with induction of remission after 12 months of treatment			
DAS28-Remission[a]	60.9%	45.2%	42.5%
Odds Ratio (95% CI) vs. MTX	2.01 (1.18, 3.43)	N/A	0.92 (0.55, 1.57)
P value	0.010	N/A	N/A
SDAI Clinical Remission[b]	42.0%	25.0%	29.3%
Estimate of Difference (95% CI) vs. MTX	17.02 (4.30, 29.73)	N/A	4.31 (-7.98, 16.61)
Boolean Clinical Remission	37.0%	22.4%	26.7%
Estimate of Difference (95% CI) vs. MTX	14.56 (2.19, 26.94)	N/A	4.31 (-7.62, 16.24)
Proportion of randomised patients in remission at 12 months and at 18 months (6 months of complete drug withdrawal)			
DAS28-Remission [a]	14.8%	7.8%	12.4%
Odds Ratio (95% CI) vs. MTX	2.51 (1.02, 6.18)	N/A	2.04 (0.81, 5.14)
P value	0.045	N/A	N/A

[a] DAS28-defined remission (DAS28-CRP <2.6)
[b] SDAI criterion (SDAI ≤ 3.3)

In SC-III the safety profiles of the three treatment groups (abatacept + MTX, abatacept monotherapy, MTX group) were overall similar. During the 12-month treatment period, adverse reactions were reported in 44.5% (53/119), 41.4% (48/116), and 44.0% (51/116) and serious adverse reactions were reported in 2.5% (3/119), 2.6% (3/116) and 0.9% (1/116) of patients treated in the three treatment groups, respectively. Serious infections were reported in 0.8% (1/119), 3.4% (4/116) and 0% (0/116) patients.

Radiographic response

Structural joint damage was assessed radiographically over a two-year period in studies II, VI, and SC-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.

In study II, 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 5. The rate of progression of structural damage in year 2 was significantly lower than that in year 1 for patients randomised to abatacept ($p < 0.0001$). Subjects entering the long term extension after 1 year of double blind treatment all received abatacept treatment and radiographic progression was investigated through year 5. Data were analyzed in an as-observed analysis using mean change in total score from the previous annual visit. The mean change was, 0.41 and 0.74 from year 1 to year 2 (n=290, 130), 0.37 and 0.68 from year 2 to year 3 (n=293, 130), 0.34 and 0.43 from year 3 to year 4 (n=290, 128) and the change was 0.26 and 0.29 (n=233, 114) from year 4 to year 5 for patients originally randomised to abatacept plus MTX and placebo plus MTX respectively.

Table 5: 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.

In study VI, the mean change in TSS at 12 months was significantly lower in patients treated with abatacept plus methotrexate compared to those treated with methotrexate plus placebo. At 12 months 61% (148/242) of the patients treated with abatacept plus methotrexate and 53% (128/242) of the patients treated with methotrexate plus placebo had no progression (TSS ≤ 0). The progression of structural damage was lower in patients receiving continuous abatacept plus methotrexate treatment (for 24 months) compared to patients who initially received methotrexate plus placebo (for 12 months) and were switched to abatacept plus methotrexate for the next 12 months. Among the patients who entered the open-label 12 month period, 59% (125/213) of patients receiving continuous abatacept plus methotrexate treatment and 48% (92/192) of patients who initially received methotrexate and switched to combination with abatacept had no progression.

In study SC-II, structural joint damage was assessed radiographically and expressed as a change from baseline in the van der Heijde-modified Total Sharp Score (mTSS) and its components. Similar inhibition was observed in both treatment groups up to 24 months (mTSS (mean ± standard deviation [SD] = 0.89 ± 4.13 vs 1.13 ±8.66), erosion score (0.41 ± 2.57 vs 0.41 ±5.04), and JSN score (0.48 ±2.18 vs 0.72 ±3.81)) for the abatacept (n=257) and adalimumab (n=260) groups, respectively.

In study SC-III, structural joint damage was assessed by MRI. The abatacept + MTX group had less progression in structural damage compared with MTX group as reflected by mean treatment difference of the abatacept + MTX group versus MTX group (Table 6).

Table 6: Structural and inflammatory MRI assessment in study SC-III

Mean Treatment Difference between Abatacept SC+MTX vs. MTX at 12 Months (95% CI)*	
MRI Erosion Score	-1.22 (-2.20, -0.25)
MRI Osteitis/Bone Oedema Score	-1.43 (-2.68, -0.18)
MRI Synovitis Score	-1.60 (-2.42, -0.78)

* n = 119 for Abatacept SC + MTX; n = 116 for MTX

Physical function response

Improvement in physical function was measured by the Health Assessment Questionnaire Disability Index (HAQ-DI) in studies II, III, IV, V, and VI and the modified HAQ-DI in study I. In study SC-I, improvement from baseline as measured by HAQ-DI at 6 months and over time was similar between subcutaneous and intravenous administration. The results from studies II, III, and VI are shown in Table 7.

Table 7: Improvement in physical function in controlled trials

	Methotrexate-Naive		Inadequate response to Methotrexate		Inadequate response to TNF Inhibitor	
	Study VI		Study II		Study III	
HAQ[c] Disability Index	Abatacept[a] +MTX	Placebo +MTX	Abatacept[a] +MTX	Placebo +MTX	Abatacept[a] +DMARDs[b]	Placebo +DMARDs[b]
Baseline (Mean)	1.7 (n=254)	1.7 (n=251)	1.69 (n=422)	1.69 (n=212)	1.83 (n=249)	1.82 (n=130)
Mean Improvement from Baseline						
Month 6	0.85 (n=250)	0.68 (n=249)	0.59*** (n=420)	0.40 (n=211)	0.45*** (n=249)	0.11 (n=130)
Month 12	0.96 (n=254)	0.76 (n=251)	0.66*** (n=422)	0.37 (n=212)	NA[e]	NA[e]
Proportion of patients with a clinically meaningful improvement[d]						
Month 6	72%[†]	63%	61%***	45%	47%***	23%
Month 12	72%[†]	62%	64%***	39%	NA[e]	NA[e]

*** $p < 0.001$, abatacept vs. placebo.
[†] $p < 0.05$, abatacept plus MTX vs MTX plus 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 periods of studies I, II, III, and VI the improvement in physical function has been maintained through 7 years, 5 years, 5 years, and 2 years, respectively.

In study SC-III, the proportion of subjects with a HAQ response as a measure of clinically meaningful improvement in physical function (reduction from baseline in HAQ-D1 score of ≥ 0.3) was greater for the abatacept+ MTX group vs. the MTX group at month 12 (65.5% vs 44.0%, respectively; treatment difference vs. MTX group of 21.6% [95% CI: 8.3, 34.9]).

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 (PCS) and the Mental Component Summary (MCS). In study VI, improvement was observed at 12 months in abatacept plus methotrexate group as compared with the methotrexate plus placebo group in both PCS and MCS, and was maintained through 2 years.

Study VII: Safety of abatacept in patients with or without washout of previous TNF-inhibitor therapy

A study of open-label intravenous abatacept on a background of nonbiologic DMARDs was conducted in patients with active RA who had an inadequate response to previous (washout for at least 2 months; n=449) or current (no washout period; n=597) TNF-inhibitor therapy (study VII). The primary outcome, incidence of AEs, SAEs, and discontinuations due to AEs during 6 months of treatment, was similar between those who were previous and current TNF-inhibitor users at enrollment, as was the frequency of serious infections.

Clinical efficacy and safety in adult psoriatic arthritis

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

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

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

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

Clinical Response

Signs and symptoms
The percent of patients achieving ACR 20, 50, or 70 responses at the recommended abatacept dose in studies PsA-I (10 mg/kg intravenous) and PsA-II (125 mg subcutaneous) are presented in Table 8 below.

Table 8: Proportion of patients with ACR responses at week 24 in studies PsA-I and PsA-II

	PsA-I[a]			**PsA-II[b,c]**		
	Abatacept 10 mg/kg IV N=40	**Placebo N=42**	**Estimate of difference (95% CI)**	**Abatacept 125 mg SC N=213**	**Placebo N=211**	**Estimate of difference (95% CI)**

Table 8: Proportion of patients with ACR responses at week 24 in studies PsA-I and PsA-II

	PsA-I[a]			PsA-II[b,c]		
ACR 20	47.5%*	19.0%	28.7 (9.4, 48.0)	39.4%*	22.3%	17.2 (8.7, 25.6)
ACR 50	25.0%	2.4%	22.7 (8.6, 36.9)	19.2%	12.3%	6.9 (0.1, 13.7)
ACR 70	12.5%	0%	12.5 (2.3, 22.7)	10.3%	6.6%	3.7 (-1.5, 8.9)

* $p < 0.05$ vs placebo, p values not assessed for ACR 50 and ACR 70.

[a] 37% of patients were previously treated with TNF inhibitor.

[b] 61% of patients were previously treated with TNF inhibitor.

[c] Patients who had less than 20% improvement in tender or swollen joint counts at Week 16 met escape criteria and were considered non-responders.

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

Higher ACR 20 responses in study PsA-II were seen with abatacept 125 mg subcutaneous vs. placebo irrespective of concomitant non-biological DMARD treatment. The ACR 20 responses with abatacept 125 mg subcutaneous vs placebo in patients who did not use non-biological DMARDs were 27.3% vs 12.1%, respectively, (15.15 [1.83, 28.47], estimate of difference [95% CI]), and in patients who had used non-biological DMARDs were 44.9% vs 26.9%, respectively, (18.00 [7.20, 28.81], estimate of difference [95% CI]). Clinical responses were maintained or continued to improve up to one year in studies PsA-I and PsA-II.

Structural response

In study PsA-II, the proportion of radiographic non-progressors (≤ 0 change from baseline) in total PsA-modified SHS on x-rays at Week 24 was greater with abatacept 125 mg subcutaneous (42.7%) than placebo (32.7%) (10.0 [1.0, 19.1] estimate of difference [95% CI]).

Physical Function Response

In study PsA-I, the proportion of patients with ≥ 0.30 decrease from baseline in HAQ-DI score was 45.0% with intravenous abatacept vs 19.0% with placebo (26.1 [6.8, 45.5], estimate of difference [95% CI]) at Week 24. In study PsA-II, the proportion of patients with at least ≥ 0.35 decrease from baseline in HAQ-DI was 31.0% with abatacept vs. 23.7% with placebo (7.2 [-1.1, 15.6], estimate of difference [95% CI]). Improvement in HAQ-DI scores was maintained or improved for up to 1 year with continuing abatacept treatment in both PsA-I and PsA-II studies.

No significant changes in PASI scores with abatacept treatment were seen over the 24-week double-blind period. Patients entering the two PsA studies had mild to moderate psoriasis with median PASI scores of 8.6 in PsA-I and 4.5 in PsA-II. In study PsA-I, the proportions of patients achieving PASI 50 response was 28.6% with abatacept vs. 14.3% with placebo (14.3 [-15.3, 43.9], estimate of difference [95% CI]), and the proportion of patients who achieved PASI 75 response was 14.3% with abatacept vs. 4.8% with placebo (9.5 [-13.0, 32.0], estimate of difference [95% CI]). In study PsA-II, the proportion of patients who achieved PASI 50 response was 26.7% with abatacept vs. 19.6% with placebo (7.3 [-2.2, 16.7], estimate of difference [95% CI]), and the proportion of patients who achieved PASI 75 response was 16.4% with abatacept vs. 10.1% with placebo (6.4 [-1.3, 14.1], estimate of difference [95% CI]).

Paediatric population in polyarticular juvenile idiopathic arthritis

Subcutaneous

The efficacy of subcutaneous abatacept in children 2 to 17 years of age is based on pharmacokinetic exposure and extrapolation of established efficacy from intravenous abatacept in pJIA patients and subcutaneous abatacept in adult patients with RA, and is supported by data from an ongoing clinical study. In this study children and adolescents with moderately to severely active pJIA, ages 2 to 17 years (46 patients in the 2 to 5 year age cohort and 173 patients in the 6 to 17 year age cohort) with an inadequate response or intolerance to at least one DMARD, which may have included biologic agents, were treated. The safety and efficacy of subcutaneous abatacept were assessed in a single-arm, open-label study designed with a primary endpoint of steady-state trough concentration (c_{min}) at 4 months (short-term period) in the 6 to 17 year age cohort. Patients continued abatacept treatment in an ongoing open-label extension, which assessed long-term safety and efficacy for an additional 20 months.

At baseline 79% of 219 patients enrolled and treated in the study were taking methotrexate (mean dose at study entry, 12.3 mg/m^2/week) and 21% of patients received abatacept monotherapy. Of the 219 patients entering the study, 56 (25.6%) had previously been treated with biologic DMARD therapy (including TNF inhibitors and tocilizumab).

Patients entered in the trial were a mean 10.6 years of age with mean disease duration of 2.4 years. They had active disease, with a mean active joint count of 11.8, mean number of joints with loss of motion of 10.3, and a mean elevated C-reactive protein (CRP) level of 1.24 mg/dL at baseline.

Of the 219 patients treated, 205 completed the short-term period and 200 entered the ongoing long-term extension period. In the 2 to 5 year age cohort, 39 (84.8%) patients completed 2 years. In the 6 to 17 year age cohort 132 (76.3%) patients completed 2 years.

Response rates at the end of the short-term exposure are summarised in Table 9:

Table 9: Proportion (%) of polyarticular JIA patients with ACRP responses or inactive disease at end of short-term period (4 months)

	Ages 2 to 17 years
	n=219
ACRP30	84.5%
ACRP50	75.3%
ACRP70	57.1%
ACRP90	34.7%
ACRP100	20.1%
Inactive disease*	34.2%

* No active joints, physician's global assessment of disease severity ≤10 mm and CRP ≤0.6 mg/dL.

The ACRP responses and inactive disease results were maintained through 2 years.

Intravenous
Children and adolescents with moderate to severe active pJIA, ages 6 to 17 years with an inadequate response or intolerance to at least one DMARD, which may have included biologic agents, were enrolled. The safety and efficacy of intravenous abatacept were assessed in a three-part study. Period A was a 4-month open-label lead-in designed to induce an ACR Pedi 30 response. Patients achieving at least a ACR Pedi 30 response at the end of Period A were randomised into a double-blind, withdrawal phase (Period B), and received either abatacept or placebo for 6 months or until pJIA disease flare as defined in the study. Unless they had discontinued due to safety reasons, all patients who completed, or had a flare during Period B or were non-responders in Period A were offered entry into Period C, the open-label extension, which assessed long-term safety and efficacy.

In Period A all patients received 10 mg/kg of abatacept on days 1, 15, 29, 57 and 85 and were assessed on day 113. During period A, 74% were taking methotrexate (mean dose at study entry, 13.2 mg/m^2/week) thus, 26% of patients received abatacept monotherapy in Period A. Of the 190 patients entering the study, 57 (30%) had previously been treated with TNF-inhibitor therapy.

ACR Pedi 30 responders at the end of Period A were randomised into Period B, the double-blind, withdrawal phase, to receive either abatacept or placebo for 6 months or until JIA flare. Flare was defined as:
≥ 30% worsening in at least 3 of the 6 pJIA core set variables
≥ 30% improvement in not more than 1 of the 6 pJIA core set variables
≥ 2 cm (possible up to 10 cm) of worsening must have been present if the Physician or Parent Global Assessment was used to define flare
worsening in ≥ 2 joints must have been present if the number of active joints or joints with limited range of motion was used to define flare

The patients entered in the trial were a mean of 12.4 years of age with mean disease duration of 4.4 years. They had active disease, with baseline mean active joint count of 16 and a mean number of joints with loss of motion of 16; and elevated C-reactive protein (CRP) levels (mean, 3.2 mg/dl) and ESRs (mean, 32 mm/h). Their pJIA subtypes at disease onset were: oligoarticular (16%), polyarticular (64%; 20% of the total were rheumatoid factor positive), and systemic (20%).

Of the 190 patients enrolled, 170 completed Period A, 65% (123/190) achieved an ACR Pedi 30 response, and 122 were randomised to Period B. Responses were similar in all subtypes of pJIA studied and for patients with or without methotrexate use. Of the 133 (70%) patients with no prior TNF-inhibitor therapy, 101 (76%) achieved at least an ACR Pedi 30 response;

of the 57 patients who had received prior TNF-inhibitor therapy, 22 (39%) achieved at least an ACR Pedi 30 response.

During Period B, the time to disease flare for the patients randomised to placebo was significantly shorter than for those randomised to abatacept (primary endpoint, p=0.0002; log-rank test). Significantly more placebo recipients flared during Period B (33/62; 53%) than those maintained on abatacept (12/60; 20%; chi-square p<0.001). The risk of disease flare for patients continuing on abatacept was less than one third that for placebo-treated patients (hazard ratio estimate=0.31; 95% CI 0.16, 0.59).

Most randomised Period B patients entered Period C (58/60 Period B abatacept recipients; 59/62 Period B placebo recipients), as did 36 of the 47 Period A non-responders (n=153 total patients).

Response rates at the end of Period A, at the end of Period B and after 5 years exposure in Period C are summarised in Table 10:

Table 10: Proportion (%) of polyarticular JIA patients with ACR responses or inactive disease

	End of Period A (day 113)	End of Period B[a] (day 169)		Period C[b] (day 1765)		
	Abatacept	Abatacept	Placebo	Abatacept group in Period B	Placebo group in Period B	Non-responder in Period A
	n= 190	n= 58	n= 59	n= 33	n= 30	n= 13
ACR30	65	85	68	97	87	69
ACR50	50	79	53	94	80	69
ACR70	28	55	31	79	63	54
ACR90	13	41	15	67	40	39
Inactive disease	Not assessed	31	10	52	33	31

[a] day 169 Last Observation Carried Forward (LOCF) for patients treated in Period C
[b] As observed

Participants in Period C at day 1765 included 33 of the 58 Period B abatacept recipients, 30 of the 59 Period B placebo recipients, and 13 of the 36 Period A non-responders. The median duration of abatacept treatment in Period C was 1815 days (range 57–2,415 days; nearly 61 months). One hundred and two (67%) of the subjects had received at least 1,080 days (~ 36 months) of abatacept therapy in Period C. All patients had at least 4 months of prior, open-label abatacept treatment in Period A.

5.2 Pharmacokinetic properties

Adult rheumatoid arthritis

The geometric mean estimate (90% confidence interval) for the bioavailability of abatacept following subcutaneous administration relative to intravenous administration is 78.6% (64.7%, 95.6%). The mean (range) for c_{min} and c_{max} at steady state observed after 85 days of treatment was 32.5 mcg/mL (6.6 to 113.8 mcg/mL) and 48.1 mcg/mL (9.8 to 132.4 mcg/mL), respectively. Mean estimates for systemic clearance (0.28 mL/h/kg), volume of distribution

(0.11 L/kg), and terminal half-life (14.3 days) were comparable between subcutaneous and intravenous administration.

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

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

Adult psoriatic arthritis

In PsA-I, patients were randomised to receive intravenous placebo or abatacept 3 mg/kg (3/3 mg/kg), 10 mg/kg (10/10 mg/kg), or two doses of 30 mg/kg followed by 10 mg/kg (30/10 mg/kg), on day 1, 15, 29, and then every 28 days thereafter. In this study, the steady-state concentrations of abatacept were dose-related. The geometric mean (CV%) c_{min} at day 169 were 7.8 mcg/mL (56.3%) for the 3/3 mg/kg, 24.3 mcg/mL (40.8%) for 10/10 mg/kg, and 26.6 mcg/mL (39.0%) for the 30/10 mg/kg regimens.
In study PsA-II following weekly subcutaneous administration of abatacept at 125 mg, steady-state of abatacept was reached at day 57 with the geometric mean (CV%) c_{min} ranging from 22.3 (54.2%) to 25.6 (47.7%) mcg/mL on days 57 to 169, respectively.
Consistent with the results observed earlier in RA patients, population pharmacokinetic analyses for abatacept in PsA patients revealed that there was a trend toward higher clearance (L/h) of abatacept with increasing body weight.

Paediatric pJIA population

Pharmacokinetics of abatacept for subcutaneous injection have been studied in patients 2 to 17 years of age.

Steady state of abatacept was achieved by day 85 following the weekly body-weight–tiered subcutaneous abatacept dosing. Comparable trough concentrations across weight tiers and age groups were achieved by the body-weight–tiered subcutaneous dosing regimen. The mean (range) trough concentration of abatacept at day 113 was 46.2 mcg/mL (13.4 to 96.2 mcg/mL), 48.0 mcg/mL (22.4 to 122.1 mcg/mL), and 38.5 mcg/mL (9.3 to 73.2 mcg/mL) in paediatric pJIA patients weighing 10 to <25 kg, 25 to <50 kg, and ≥50 kg, respectively.

The pharmacokinetics of abatacept is similar in adult RA and paediatric pJIA patients except for the higher SC absorption in pJIA patients. SC bioavailability (F) increased by 28% and the absorption rate constant (KA) was higher in pJIA patients than RA patients.

Consistent with the intravenous-data, population pharmacokinetic analyses for subcutaneous abatacept in pJIA patients revealed that there was a trend toward higher clearance of abatacept with increasing body weight. Age and gender (when corrected for body weight) did not affect apparent clearance. Concomitant medication, such as methotrexate, corticosteroids, and NSAIDs, did not influence abatacept apparent clearance.

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 abatacept 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.

<u>Non-clinical studies relevant for use in the paediatric population</u>

Studies in rats exposed to abatacept have shown immune system abnormalities including a low incidence of infections leading to death (juvenile rats). In addition, inflammation of the thyroid and pancreas was frequently seen in both juvenile and adult rats exposed to abatacept. Juvenile rats seemed to be more sensitive to lymphocytic inflammation of thyroid. Studies in adult mice and monkeys have not demonstrated similar findings. It is likely that the increased susceptibility to opportunistic infections observed in juvenile rats is associated with the exposure to abatacept before development of memory responses. The relevance of these results to humans is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose

Poloxamer 188

Sodium dihydrogen phosphate monohydrate

Disodium phosphate anhydrous

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.

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

6.5 Nature and contents of container

ORENCIA 87.5 mg solution for injection in pre-filled syringe

0.7 mL pre-filled syringe (type 1 glass) with an automatic needle safety guard and flange extenders (light blue plunger).

Packs of 4 pre-filled syringes with needle guard.

Not all pack-sizes may be marketed.

6.6 Special precautions for disposal and other handling

The medicinal product is for single use only. After removing the pre-filled syringe from the refrigerator the pre-filled syringe should be allowed to reach room temperature by waiting 30 minutes, before injecting ORENCIA. The syringe should not be shaken.

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

7 MARKETING AUTHORISATION HOLDER

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