

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ORENCIA[®] 250 mg (Lyophilisate for solution for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of ORENCIA 250 mg provides 250 mg of abatacept.

ORENCIA contains 500 mg maltose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Lyophilisate for solution for infusion.

Lyophilised powder: White to off-white, whole or fragmented cake.

ORENCIA is supplied as a sterile, white, preservative-free, lyophilised powder for parenteral administration.

Following reconstitution with 10 ml of sterile water for injection, the solution of ORENCIA is clear, colourless to pale yellow, with a pH range of 7,2 – 7,8.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adult rheumatoid arthritis (RA)

ORENCIA is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with active rheumatoid arthritis. ORENCIA may be used as monotherapy or concomitantly with DMARDs (disease modifying anti-rheumatic drugs) other than tumour necrosis factor (TNF) blocking agents.

Juvenile idiopathic arthritis (JIA)

ORENCIA is indicated for reducing signs and symptoms in paediatric patients 6 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis.

ORENCIA may be used as an adjunct therapy with other antirheumatic agents.

ORENCIA should not be administered concomitantly with TNF antagonists. ORENCIA is not recommended for use concomitantly with other biologic rheumatoid arthritis therapy such as anakinra.

4.2 Posology and method of administration

Posology

ORENCIA should NOT be used with siliconised syringes.

For adult patients with RA, ORENCIA should be administered as a 30 minute intravenous infusion utilising the weight range-based dosing specified in **Table 1**. Following the initial administration, ORENCIA should be given at 2 and 4 weeks after the first infusion, and every 4 weeks thereafter. ORENCIA may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.

For paediatric juvenile idiopathic arthritis, a dose calculated based on each patient's body weight is used (see below under Paediatric and adolescent).

Table 1: Dose of ORENCIA		
Body Weight of Patient	Dose	Number of Vials ^a
< 60 kg	500 mg	2
60 to 100 kg	750 mg	3
> 100 kg	1 g	4

^a Each vial provides 250 mg of abatacept for administration.

Special populations

Renal impairment, hepatic impairment

As ORENCIA has not been studied in these patients, no dose recommendations can be made.

Geriatric

No dose adjustment is required.

Paediatric and adolescent population

Juvenile Idiopathic Arthritis: The recommended dose of ORENCIA for patients 6 to 17 years of age with juvenile idiopathic arthritis who weigh less than 75 kg is 10 mg/kg calculated based on the patient's body weight at each administration.

Paediatric patients weighing 75 kg or more should be administered ORENCIA following the adult dosing regimen, not to exceed a maximum dose of 1000 mg. ORENCIA should be administered as a 30-minute intravenous infusion.

Following the initial administration, ORENCIA should be given at 2 and 4 weeks after the first infusion and every 4 weeks thereafter. Any unused portions in the vials must be immediately discarded. (See section 4.4).

Concomitant therapy

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

Method of administration

Use aseptic technique.

ORENCIA is provided as a lyophilised powder in preservative-free, single-use vials. Each vial of ORENCIA must be reconstituted with 10 ml of sterile water for injection. Immediately after reconstitution, the product must be further diluted to 100 ml with 0,9 % sodium chloride injection. The infusion of the fully diluted ORENCIA solution must be completed within 24 hours of reconstitution of the ORENCIA vials. The fully diluted ORENCIA solution may be stored at room temperature (up to 25 °C) or refrigerated at 2 °C to 8 °C before use (see section 6.3).

Refer to **Table 1** for the dose and number of ORENCIA vials required. Each ORENCIA vial provides 250 mg of abatacept for administration.

Reconstitute the ORENCIA powder in each vial with 10 ml of sterile water for injection using the SILICONE-FREE DISPOSABLE SYRINGE PROVIDED WITH EACH VIAL and an 18-21 gauge needle.

Remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of sterile water for injection to the glass wall of the vial. Do not use the vial if the vacuum is not present.

To minimise foam formation in solutions of ORENCIA, the vial should be rotated with gentle swirling until the contents are completely dissolved. Avoid prolonged or vigorous agitation. DO NOT SHAKE. Upon complete dissolution of the lyophilised powder, the vial should be vented with a needle to dissipate any foam that may be present. The solution should be clear and colourless to pale yellow.

Do not use if opaque particles, discolouration, or other foreign particles are present. After reconstitution, the concentration of abatacept in the vial will be 25 mg/ml.

The reconstituted ORENCIA solution must be further diluted to 100 ml as follows: From a 100 ml infusion bag or bottle, withdraw a volume of 0,9 % sodium chloride injection 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 a SILICONE-FREE DISPOSABLE SYRINGE PROVIDED WITH EACH VIAL. Gently mix. DO NOT SHAKE THE BAG OR BOTTLE. The concentration of the fully diluted ORENCIA solution in the infusion bag or bottle will be approximately 5, 7,5 or 10 mg of abatacept per ml of solution depending on whether 2, 3 or 4 vials of ORENCIA are used. Any unused portions in the vials must be immediately discarded.

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).

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

4.3 Contraindications

- ORENCIA should not be administered to patients with known hypersensitivity to ORENCIA or any of its components.
- Active or dormant untreated tuberculosis.
- ORENCIA should NOT be used during pregnancy or if a woman plans to become pregnant, or by mothers who are breastfeeding their infants (see section 4.6).

4.4 Special warnings and precautions for use

Combination with TNF blocking agents

There is limited experience with the use of ORENCIA in combination with TNF blocking agents.

In intravenous placebo-controlled clinical trials in patients with adult RA, patients receiving concomitant ORENCIA and TNF blocking agent therapy experienced more infections (24 %) and serious infections (2,2 %) compared to patients treated with only TNF blocking agents (19 % and 0,8 %, respectively). Concurrent therapy with ORENCIA and a TNF blocking agent is not recommended.

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

Hypersensitivity

Hypersensitivity reactions including anaphylactic reactions have been reported with intravenous ORENCIA administration, in clinical trials, where patients were not required to be pretreated to prevent hypersensitivity reactions.

Other events potentially associated with medicine hypersensitivity, such as hypotension, urticaria, and dyspnoea that occurred within 24 hours of ORENCIA infusion, may occur.

Anaphylaxis or anaphylactoid reactions can occur after the first infusion and can be life-threatening. In postmarketing experience, a case of fatal anaphylaxis following the first infusion of ORENCIA has been reported. If an anaphylactic or other serious allergic reaction occurs, administration of IV ORENCIA should be stopped immediately with appropriate therapy instituted, and the use of ORENCIA should be permanently discontinued.

Effects on the immune system

The possibility exists for ORENCIA to affect vaccination responses and host defenses against infections and malignancies.

Infections

Serious infections, including sepsis and pneumonia, have been reported in patients receiving ORENCIA. Some of these infections have been fatal.

Medical practitioners should exercise caution when considering the use of ORENCIA in patients with a history of recurrent infections, underlying conditions which may predispose them to infections, or chronic, latent, or localised infections.

Patients who develop a new infection while undergoing treatment with ORENCIA should be monitored closely. **Administration of ORENCIA should be discontinued if a patient develops a serious infection.**

A higher rate of serious infections has been observed in adult RA patients treated with concurrent TNF blocking agents and ORENCIA.

When treating patients with therapies that modulate the immune system, it is appropriate to screen and monitor for tuberculosis infections. ORENCIA has not been studied in patients with a positive tuberculosis screen, and the safety of ORENCIA in individuals with latent tuberculosis is unknown (see section 4.3).

Before starting treatment with ORENCIA, all patients must be evaluated for both active and inactive (“latent”) tuberculosis. This evaluation should include a detailed medical history with personal history of tuberculosis

or possible previous contact with tuberculosis and previous and/or current immunosuppressive therapy.

Appropriate screening tests, i.e. tuberculin skin test and chest x-ray should be performed in all patients (local recommendations may apply).

Prescribers are reminded of the risk of false negative tuberculin skin test results especially in patients who are severely ill or immunocompromised. If active tuberculosis is diagnosed, ORENCIA treatment should not be initiated (see section 4.3).

If inactive (“latent”) tuberculosis is diagnosed, prophylactic anti-tuberculosis therapy must be started before the initiation of ORENCIA, and in accordance with local recommendations.

In this situation, the benefit/risk balance of ORENCIA therapy should be carefully considered. Patients must be monitored closely for infections, including miliary tuberculosis, while on and after treatment with ORENCIA.

In clinical trials with ORENCIA, patients were not screened for HIV infection, however patients with known HIV infection were excluded from study.

Anti-rheumatic therapies have been associated with hepatitis B reactivation. Therefore, screening for viral hepatitis should be performed in accordance with guidelines before starting therapy with ORENCIA. In clinical studies with ORENCIA, patients who screened positive for hepatitis were excluded from study.

Progressive multifocal leukoencephalopathy (PML)

Cases of progressive multifocal leukoencephalopathy (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

The potential role of long-term use (> 42 months) of ORENCIA in the development of malignancies in humans is unknown.

The frequencies of malignancies in the placebo-controlled clinical trials in adult RA up to 14 months were similar for ORENCIA-treated patients and placebo-treated patients (1,2 % and 0,9 %, respectively) (see section 4.8).

There have been reports of non-melanoma skin cancers in patients receiving ORENCIA. Periodic skin examinations are recommended for all patients, particularly those with risk factors for skin cancer.

Immunisations

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. Medicines that affect the immune system, including ORENCIA, may blunt the effectiveness of some immunisations.

Patients treated with TRADEMARK may receive concurrent non-live vaccines.

Responses to pneumococcal and inactivated influenza vaccines have been studied in subjects receiving ORENCIA. Pneumococcal vaccination with the standard 23-valent vaccine was studied in healthy subjects to assess the effect of ORENCIA on the antibody response to pneumococcal vaccine. This study suggested that ORENCIA may blunt the effectiveness of the immune response but did not significantly inhibit the ability of healthy subjects to develop a clinically significant or positive immune response (at least a 2-fold increase above baseline) to 23-valent pneumococcal vaccines. ORENCIA was evaluated in an open-label study in RA patients administered the 23-valent pneumococcal vaccine. After pneumococcal vaccination, a majority of ORENCIA-treated patients (62/112) were able to mount an adequate immune response of at least a 2-fold increase in antibody titers to pneumococcal polysaccharide vaccine.

ORENCIA 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 ORENCIA-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.

It is recommended that patients with juvenile idiopathic arthritis be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating ORENCIA therapy.

Blood glucose testing

The glucose dehydrogenase pyrroloquinolinequinone (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. Patients that require blood glucose monitoring should be advised to consider methods that do not react with maltose. **For details on blood glucose determining tests, the local laboratories should be contacted.**

Paediatric use

The safety and efficacy of ORENCIA in paediatric patients below 6 years of age have not been established.

Therefore, ORENCIA is not recommended for use in patients below the age of 6 years.

Safety and efficacy of ORENCIA in paediatric patients for uses other than juvenile idiopathic arthritis have not been established.

4.5 Interaction with other medicines and other forms of interaction

Formal interaction studies have not been conducted with ORENCIA.

Concurrent administration of a TNF blocking agent with ORENCIA has been associated with an increased risk of serious infections. Concurrent therapy with ORENCIA and TNF blocking agents is not recommended.

There is insufficient experience to assess the safety and efficacy of ORENCIA administered concurrently with other biologic rheumatoid arthritis therapy, such as anakinra, and therefore such use is not recommended.

ORENCIA has not been studied in combination with agents which deplete lymphocyte count. Such combination therapy could potentiate the effects of ORENCIA on the immune system.

Effect of other medicines on abatacept

The majority of patients in the placebo-controlled clinical trials received concomitant DMARDs, NSAIDs, and/or corticosteroids. Most patients were taking MTX. Other less frequently used concomitant DMARDs included chloroquine/hydroxychloroquine, sulfasalazine and leflunomide. There is limited experience with abatacept in combination with other DMARDs such as azathioprine, gold and anakinra.

Population pharmacokinetic analyses revealed that MTX, NSAIDs, corticosteroids, and TNF blocking agents did not influence abatacept clearance.

Other interactions

Blood Glucose Testing: Parenteral medicines 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 only use methods that do not react with maltose**, such as those based on glucose dehydrogenase nicotinic adenine dinucleotide (GDH-NAD), glucose oxidase, or glucose hexokinase test methods (see section 4.4 *Blood Glucose Testing*).

4.6 Fertility, pregnancy and lactation**Pregnancy**

There are no studies in pregnant women. ORENCIA should NOT be used during pregnancy, or if a woman is planning to become pregnant.

Abatacept may cross the placenta into the serum of infants born to women treated with abatacept during pregnancy. Consequently, these infants may be at increased risk for infection. The safety of administering live vaccines to infants exposed to abatacept *in utero* is unknown. Administration of live vaccines to infants exposed to abatacept *in utero* is not recommended for 10 weeks following the mother's last exposure to abatacept during pregnancy

Breastfeeding

Abatacept has been shown to be present in rat milk. It is not known whether abatacept is excreted in human milk. Mothers should be instructed not to breastfeed if they are receiving ORENCIA.

4.7 Effects on ability to drive and use machines

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

CLINICAL TRIAL EXPERIENCE IN ADULT RA

ORENCIA has been studied in patients with active rheumatoid arthritis in placebo-controlled clinical trials (2653 patients with ORENCIA, 1485 with placebo).

In placebo-controlled clinical trials with ORENCIA administered intravenously, adverse drug reactions (ADRs) (adverse events at least possibly causally-related to treatment) were reported in 49,4 % of ORENCIA-treated patients and 45,8 % of placebo-treated patients. The most frequently reported ADRs (≥ 5 %) among ORENCIA-treated patients were headache and nausea.

The proportion of patients who discontinued treatment due to ADRs was 3,0 % for ORENCIA-treated patients and 2,0 % for placebo-treated patients.

Listed below are ADRs that occurred with greater frequency (difference $> 0,2$ %) in ORENCIA-treated patients than in placebo-treated patients. Also listed are ADRs from clinical trials at least possibly causally-related to ORENCIA displayed by system organ class and frequency.

The list is presented by system organ class and frequency, using the following categories: very common (≥ 10 %); common (≥ 1 %; < 10 %); uncommon ($\geq 0,1$ %; < 1 %); rare ($\geq 0,01$ %; $< 0,1$ %).

Side Effects in Placebo-Controlled Trials

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
	Uncommon	Tooth infection, infected skin ulcer, onychomycosis, rhinitis, ear infection, pyelonephritis.
Neoplasms benign and malignant (including cysts and polyps)	Uncommon	Basal cell carcinoma
Blood and the 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	Paraesthesia
Eye disorders	Uncommon	Conjunctivitis, reduced visual acuity
Ear and labyrinth disorders	Uncommon	Vertigo
Cardiac disorders	Uncommon	Tachycardia, bradycardia, palpitations
Vascular disorders	Common	Hypertension
	Uncommon	Hypotension, hot flush, flushing
Respiratory, thoracic and mediastinal disorders	Common	Cough
	Uncommon	Chronic obstructive pulmonary disease exacerbation
Gastrointestinal disorders	Common	Abdominal pain, diarrhoea, nausea, dyspepsia, mouth

		ulceration, aphthous stomatitis
	Uncommon	Gastritis
Skin and subcutaneous tissue disorders	Common	Rash (including dermatitis),
	Uncommon	Increased tendency to bruise, alopecia, dry skin, hyperhidrosis, erythema, acne
Musculoskeletal, connective tissue and bone disorders	Uncommon	Arthralgia, pain in extremity
Reproductive system and breast disorders	Uncommon	Amenorrhoea, menorrhagia
General disorders and administration site conditions	Common	Fatigue, asthenia
	Uncommon	Influenza-like illness
Investigations	Common	Increased blood pressure, abnormal liver function test (including increased transaminases)
	Uncommon	Decreased blood pressure, increased weight

Infections

In the placebo-controlled trials with durations of 6 to 14 months, infections at least possibly related to treatment were reported in 22,7 % of ORENCIA-treated patients and 20,5 % of placebo patients.

Serious infections at least possibly related to treatment were reported in 1,5 % of ORENCIA-treated patients and 1,1 % of placebo patients. The type and frequency of serious infections was similar between the TRADEMARK and placebo treatment groups.

Malignancies

In placebo-controlled clinical trials with durations of up to 14 months, malignancies were reported in 1,2 %

(31/2653) of ORENCIA-treated patients and in 0,9 % (14/1485) of placebo-treated patients.

In the cumulative period in 7044 patients treated with ORENCIA during 21011 patient-years the incidence rate of malignancy was 1,2 (1,1, 1,4) per 100 patient-years, and the annualised incidence rate 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, 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 solid organ cancer in 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 haematologic 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

Infusion-related reactions and hypersensitivity reactions

In the clinical studies with ORENCIA, pre-medication to prevent hypersensitivity was not required. Acute infusion-related events (reported within 1 hour of the start of the infusion) were more common in the ORENCIA-treated patients than the placebo patients (5,2 % for ORENCIA, 3,7 % for placebo).

The most frequently reported event (> 1,0 %) was dizziness (1,5 % for ORENCIA, 1,0 % for placebo).

Acute infusion-related events that were reported in > 0,1 % and ≤ 1 % of patients treated with ORENCIA included cardiopulmonary symptoms such as hypotension, decreased blood pressure, tachycardia, bronchospasm, and dyspnoea; other symptoms included myalgia, nausea, erythema, flushing, urticaria, hypersensitivity, pruritus, throat tightness, chest discomfort, chills, infusion site extravasation, infusion site pain, infusion site swelling, infusion related reaction, and rash. Most of these reactions were mild to moderate.

In ORENCIA and placebo groups, there were discontinuations due to an acute infusion-related event (0,3 % for ORENCIA, 0,1 % for placebo).

Cases of hypersensitivity have been reported, including anaphylactic reactions. Other events potentially associated with medicine hypersensitivity, such as hypotension, urticaria, and dyspnoea, that occurred within 24 hours of ORENCIA infusion, have also been reported.

Adverse medicine reactions in patients with chronic obstructive pulmonary disease (COPD)

In one study, there were 37 patients with COPD treated with ORENCIA and 17 treated with placebo. The adult COPD patients treated with ORENCIA developed adverse drug reactions more frequently than those treated with placebo (51,4 % vs. 47,1 %, respectively).

Respiratory disorders occurred more frequently in ORENCIA-treated patients than in placebo-treated patients (10,8 % vs. 5,9 %, respectively); these included COPD exacerbation and dyspnoea.

A greater percentage of ORENCIA-treated than placebo-treated patients with COPD developed a serious adverse reaction (5,4 % vs. 0 %), including COPD exacerbation (1 of 37 patients [2,7 %]) and bronchitis (1 of 37 patients [2,7 %]).

Autoimmune processes

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

The incidence rate of autoimmune disorders in abatacept-treated patients during the double-blind period was 8,8 (7,6, 10,1) per 100 patient-years of exposure and for placebo-treated patients was 9,6 (7,9, 11,5) per 100 patient-years of exposure. The incidence rate in abatacept-treated patients was 3,8 per 100 patient-years in the cumulative period. The most frequently reported autoimmune-related disorder other than the indication being studied during the cumulative period were psoriasis, rheumatoid nodule, and Sjogren's syndrome.

Immunogenicity

Antibodies directed against the abatacept molecule were assessed by ELISA assays in rheumatoid arthritis patients treated for up to 8 years with abatacept. One hundred and eighty-seven of 3877 (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 1888 (5,5 %) were seropositive.

Samples with confirmed binding activity to CTLA-4 were assessed for the presence of neutralising antibodies.

Twenty-two of 48 evaluable patients showed significant neutralising activity. **Overall, there was no**

apparent correlation of antibody development to clinical response or adverse events. However, the number of patients that developed antibodies was insufficient to draw any conclusion.

Laboratory findings

Based on the results of clinical studies, no special laboratory evaluations are necessary in addition to careful medical management and supervision of patients.

Geriatric use

A total of 404 patients 65 years of age and older, including 67 patients 75 years and older, received ORENCIA in placebo-controlled clinical studies.

Similar efficacy was observed in these patients and younger patients. The frequency of serious infection and malignancy among ORENCIA-treated patients over age 65 was higher than for those under age 65.

Because there is a higher incidence of infections and malignancies in the elderly population in general, caution should be used when treating the elderly.

CLINICAL TRIAL EXPERIENCE IN JUVENILE IDIOPATHIC ARTHRITIS

The adverse reactions in paediatric patients were similar in type to those seen in adult patients (see section 4.4).

ORENCIA has been studied in 190 paediatric patients, 6 to 17 years of age, with polyarticular juvenile idiopathic arthritis. Adverse reactions that occurred at a prevalence of at least 5 % in the 4-month, lead-in, open-label period of the study were headache, nausea, diarrhoea, cough, upper respiratory tract infection, pyrexia, nasopharyngitis, and abdominal pain. One serious adverse reaction (varicella infection) was reported during the initial 4 months of treatment with ORENCIA.

Immunogenicity

Antibodies directed against the entire abatacept molecule or to the CTLA-4 portion of abatacept were assessed by ELISA assays in patients with polyarticular JIA following repeated treatment with ORENCIA.

The rate of seropositivity while patients were receiving ORENCIA therapy was 0,5 % (1/189) during Period A; 13,0 % (7/54) during Period B; and 11,4 % (17/149) during Period C. For patients in Period B who were randomised to placebo (therefore withdrawn from therapy for up to 6 months) the rate of seropositivity was 40,7 % (22/54). Anti-abatacept antibodies were generally transient and of low titer.

The absence of concomitant methotrexate (MTX) did not appear to be associated with a higher rate of seropositivity in Period B placebo recipients. The presence of antibodies was not associated with adverse reactions or infusional reactions, or with changes in efficacy or serum abatacept concentrations.

Postmarketing experience

Adverse reactions have been reported during the post-approval use of ORENCIA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to ORENCIA. During postmarketing experience, systemic infusion reactions was similar to that seen in the clinical trial experience with IV ORENCIA with the exception of one case of fatal anaphylaxis.

In the post-marketing setting, cases of non-melanoma skin cancer (including basal cell carcinoma and squamous cell carcinoma) have been reported in patients treated with abatacept. A risk for the development of non-melanoma skin cancer in patients treated with abatacept cannot be excluded.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who.umc.org) found on SAHRPA website.

4.9 Overdose

Doses up to 50 mg/kg have been administered intravenously without apparent toxic effect.

In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse

reactions and appropriate symptomatic treatment instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti Rheumatics (anti-inflammatory agents).

ORENCIA (abatacept), a selective costimulation modulator, is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to the modified Fc (hinge, CH2, and CH3 domains) portion of human immunoglobulin G1.

Abatacept is produced by recombinant DNA technology in a mammalian cell expression system.

The apparent molecular weight of abatacept is 92 kilodaltons.

Mechanism of action

By specifically binding to CD80 and CD86 on antigen presenting cells, abatacept selectively modulates a key costimulatory signal required for full activation of T lymphocytes expressing CD28.

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 attenuates T lymphocyte dependent antibody responses and inflammation. *In vitro*, abatacept attenuates T lymphocyte activation as measured by decreased proliferation and cytokine production in human lymphocytes. Abatacept decreases antigen specific TNF- α , interferon- γ , and interleukin-2 production by T lymphocytes.

In a rat collagen-induced arthritis model, abatacept suppresses inflammation, decreases anti-collagen antibody production and reduces antigen specific production of interferon- γ .

5.2 Pharmacokinetic properties

Healthy adults and adult RA:

Absorption

Abatacept is administered intravenously.

Distribution

The pharmacokinetics of abatacept were studied in healthy adult subjects after a single 10 mg/kg intravenous infusion and in RA patients after multiple 10 mg/kg intravenous infusions (see **Table 2**).

Table 2: Pharmacokinetic Parameters (Mean, Range) in Healthy Adult Subjects and RA Patients after 10 mg/kg intravenous infusion(s)		
PK Parameter	Healthy Subjects (After 10 mg/kg Single Dose) n=13	RA Patients (After 10 mg/kg Multiple Doses ^a) n=14
Peak Concentration (C_{max}) [mcg/ml]	292 (175 - 427)	295 (171 - 398)
Terminal half-life ($t_{1/2}$) [days]	16,7 (12 - 23)	13,1 (8 - 25)
Systemic clearance (Cl) [ml/h/kg]	0,23 (0,16 - 0,30)	0,22 (0,13 - 0,47)
Volume of distribution (V_{ss}) [l/kg]	0,09 (0,06 - 0,13)	0,07 (0,02 - 0,13)

^a Multiple intravenous infusions were administered at days 1, 15, 30, and monthly thereafter.

The pharmacokinetics of abatacept in adult RA patients and healthy subjects appeared to be comparable. In adult RA patients, after multiple intravenous infusions, the pharmacokinetics of abatacept showed proportional increases of C_{max} and AUC over the dose range of 2 mg/kg to 10 mg/kg.

At 10 mg/kg, serum concentration appeared to reach a steady-state by day 60 with a mean (range) trough concentration of 24 (1 - 66) mcg/ml. No systemic accumulation of abatacept occurred upon continued repeated treatment with 10 mg/kg at monthly intervals in adult RA patients.

Population pharmacokinetic analyses in adult RA patients revealed that there was a trend toward higher clearance of abatacept with increasing body weight. Age and gender (when corrected for body weight) did

not affect clearance. Concomitant methotrexate, NSAIDs, corticosteroids, and TNF blocking agents did not influence abatacept clearance.

Biotransformation and elimination

There are no studies to evaluate the metabolism or elimination of abatacept in humans. Owing to steric and hydrophilic considerations, abatacept would not be metabolised by liver cytochrome P450 enzymes. Because of its large molecular weight abatacept is not expected to undergo renal elimination.

Special populations

No formal studies were conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of abatacept.

Juvenile idiopathic arthritis

Population pharmacokinetic analysis of abatacept serum concentration data from patients with JIA aged 6 to 17 years following administration of abatacept 10 mg/kg revealed that the estimated clearance of abatacept, when normalised for baseline body weight, was higher in JIA patients (0,44 ml/h/kg) versus adult RA patients (0,3 ml/h/kg). After accounting for the effect of body weight, the clearance of abatacept was not related to age or gender. Mean estimates for distribution volume and elimination half-life were 0,12 l/kg and 11,2 days, respectively.

As a result of the higher body-weight normalised clearance in JIA patients, the observed overall systemic exposure of abatacept was lower on average than that observed in adults, such that the observed mean (range) peak and trough concentrations were 217 (58 to 700) and 11,9 (0,15 to 44,6) mcg/ml, respectively, in JIA patients who received 10 mg/kg abatacept compared to 235 (80 to 599) and 12,8 (0,61 to 51,6) mcg/ml, respectively, in adult RA patients who received body-weight-tiered doses of abatacept approximating 10 mg/kg.

Administration of other concomitant medications such as methotrexate, corticosteroids, and NSAIDs did not influence the clearance of abatacept in JIA patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maltose monohydrate

Monobasic sodium phosphate

Sodium chloride

6.2 Incompatibilities

ORENCIA should NOT be used with siliconised syringes (see section 4.2).

6.3 Shelf life

36 Months

The fully reconstituted solution may be stored at room temperature (up to 25 °C) or refrigerated at 2 °C to 8 °C before use.

Do not freeze the reconstituted solution. The reconstituted solution must be used within 24 hours of reconstitution.

6.4 Special precautions for storage

Protect the vials from light by storing in the original package until time of use. ORENCIA lyophilised powder must be refrigerated at 2 °C to 8 °C. For storage of the fully diluted ORENCIA solution see section 6.3.

6.5 Nature and contents of container

ORENCIA lyophilised powder for intravenous infusion is supplied as an individually packaged, single-use transparent type I glass vial with a polypropylene silicone-free disposable syringe. The product is available in a 15 ml vial providing 250 mg of abatacept.

6.6 Special precautions for disposal and other handling

For reconstitution of the ORENCIA lyophilized powder and subsequent dilution, use only the silicone-free disposable syringe provided with each vial of ORENCIA. Do not use a siliconized syringe. Avoid prolonged or vigorous agitation. The entire, fully diluted ORENCIA solution 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) (see section 4.2, Method of administration). Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd.*

100 Sovereign Drive

Route 21 Corporate Park

Nellmapius Drive

Irene

Pretoria, 0157

8. REGISTRATION NUMBER(S)

41/3.1/1061

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04 December 2009

10. DATE OF REVISION OF THE TEXT

20 January 2026

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