APPROVED PACKAGE INSERT

SCHEDULING STATUS S4

PROPRIETARY NAME AND DOSAGE FORM

ORENCIA® 125 mg Solution for subcutaneous injection

This formulation is not suitable for IV injection.

COMPOSITION

Each pre-filled syringe of ORENCIA 125 mg Solution for subcutaneous injection contains 125 mg abatacept. Contains sucrose.

List of excipients: anhydrous disodium phosphate, poloxamer 188, sodium phosphate monobasic monohydrate, sucrose and water for injection.

PHARMACOLOGICAL CLASSIFICATION

A 3.1 Anti Rheumatics (anti-inflammatory agents)

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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.

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 naïve 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 TNFα, 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.

Pharmacokinetic properties

Abatacept exhibited linear pharmacokinetics following subcutaneous administration.

The mean (range) for C_{min} and C_{max} at steady state observed after 85 days of weekly treatment with 125 mg, was 32,5 μg/ml (6,6 to 113,8 μg/ml) and 48,1 μg/ml (9,8 to 132,4 μg/ml), respectively. The bioavailability of abatacept following subcutaneous administration relative to intravenous administration is 78,6 %. 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 SC and IV administration.

A single study was conducted to determine the effect of monotherapy use of abatacept in immunogenicity following subcutaneous administration without an IV load. When the IV loading dose was not administered, a mean trough concentration of 12,6 μg/ml was achieved after 2 weeks of dosing. The efficacy response over time in this study appeared consistent with studies that included an IV loading dose, however, the effect of no IV load on the onset of efficacy has not been formally studied.

Consistent with the IV data, population pharmacokinetic analyses for SC 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 methotrexate (MTX), non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and TNF (tumour necrosis factor) blocking agents did not influence abatacept apparent clearance.

Metabolism and elimination

There are no studies to evaluate the metabolism or elimination of abatacept in humans. Owing to stearic 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.

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.

Paediatrics and Adolescents

The safety and efficacy of ORENCIA subcutaneous administration in children below 18 years of age have not been established. No data are available.

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 PREGNANCY AND LACTATION).

WARNINGS AND SPECIAL PRECAUTIONS

ORENCIA 125 mg Solution for subcutaneous injection has not been studied in juvenile idiopathic arthritis.

Combination with TNF blocking agents

ORENCIA should not be administered concomitantly with TNF blocking agents.

There is limited experience with the use of ORENCIA in combination with TNF blocking agents. In placebo-controlled clinical trials in patients with adult RA, patients receiving concomitant intravenous 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.

Combination with other biologic agents

ORENCIA is not recommended for use concomitantly with other biologic rheumatoid arthritis therapy, such as anakinra.

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 hypersensitivity, such as hypotension, urticaria, and dyspnoea that occurred within 24 hours of ORENCIA infusion, may occur.

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 CONTRAINDICATIONS).

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 CONTRAINDICATIONS).

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.

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 short-term clinical trials in adult RA up to 12 months were 1,4 % for ORENCIA-treated patients and 1,1 % for placebo-treated patients. (Refer to SIDE EFFECTS).

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. No data are available on the effects of vaccinations in patients receiving ORENCIA. Medicines that affect the immune system, including ORENCIA, may blunt the effectiveness of some immunisations.

Paediatrics and adolescents

The safety and efficacy of ORENCIA 125 mg solution for subcutaneous injection in children below 18 years of age have not been established. No data are available.

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 machines should be avoided.

Sucrose

Contains sucrose, which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrose-isomaltase insufficiency should not receive ORENCIA.

INTERACTIONS

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 (disease modifying anti-rheumatic drugs), 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.

PREGNANCY AND LACTATION

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

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.

DOSAGE AND DIRECTIONS FOR USE

Recommended dosage

ORENCIA 125 mg solution for subcutaneous injection should be administered weekly at a dose of 125 mg by subcutaneous injection regardless of weight and used with or without an IV loading dose (see PHARMACOLOGICAL

ACTION, Pharmacokinetic properties). For patients initiating therapy with an IV loading dose, ORENCIA should be initiated with a single intravenous infusion followed by the first 125 mg subcutaneous injection and then by subcutaneous injection once a week thereafter (please refer to **Dosage and Directions for use** for IV loading dose in the Package Insert of abatacept 250 mg lyophilisate solution for infusion).

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

Renal impairment, hepatic impairment

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

Paediatric and adolescent

The safety and efficacy of ORENCIA subcutaneous administration in children below 18 years of age have not been established. No data are available.

Geriatric

No dose adjustment is required.

Concomitant therapy

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

Preparation and administration instructions for subcutaneous administration

ORENCIA solution for subcutaneous injection is not intended for IV infusion.

ORENCIA solution for subcutaneous injection is intended for use under the guidance of a medical practitioner or healthcare practitioner. After proper training in subcutaneous injection technique, a patient may self-inject with ORENCIA solution for subcutaneous injection if a doctor determines that it is appropriate.

Patients should be instructed to follow the detailed ***"Instructions for preparing and giving a subcutaneous injection of ORENCIA"*** provided at the end of the Patient Information Leaflet.

ORENCIA should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.
Do not use ORENCIA prefilled syringes exhibiting particulate matter or discolouration.
ORENCIA solution for subcutaneous injection should be clear to slightly opalescent and colourless to pale yellow. Any leftover product remaining in the prefilled syringe should not be used.
Patients using ORENCIA solution for subcutaneous injection should be instructed to inject the full amount in the syringe (1,0 ml), which provides 125 mg of ORENCIA, according to the directions provided in the Patient Information Leaflet.
Injection sites should be rotated and injections should never be given into areas where the skin is tender, bruised, red or hard.

SIDE EFFECTS

Listed below are ADRs that occurred with greater frequency (difference > 0,2 %) in ORENCIA-treated patients than in placebo-treated patients.

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

Side Effects in Placebo-Controlled Trials

Infections and infestations	Common	Lower respiratory tract infection (including bronchitis), urinary tract infection, herpes simplex, upper respiratory tract infection (including tracheitis, nasopharyngitis), rhinitis
	Uncommon	Tooth infection, infected skin ulcer, onychomycosis, pelvic inflammatory disease
Neoplasms benign and malignant (including cysts and polyps)	Uncommon	Basal cell carcinoma
Blood and the lymphatic system disorders	Uncommon	Thrombocytopenia, leukopenia
Psychiatric disorders	Uncommon	Depression, anxiety
Nervous system disorders	Very Common	Headache
	Common	Dizziness
	Uncommon	Paraesthesia
Eye disorders	Uncommon	Conjunctivitis, reduced visual acuity

Ear and labyrinth disorders	Uncommon	Vertigo
Cardiac disorders	Uncommon	Tachycardia, bradycardia, palpitations
Vascular disorders	Common	Hypertension, flushing
	Uncommon	Hypotension, hot flush
Respiratory, thoracic and mediastinal disorders	Common	Cough
Gastrointestinal disorders	Common	Abdominal pain, diarrhoea, nausea, dyspepsia
	Uncommon	Gastritis, mouth ulceration, aphthous stomatitis
Skin and subcutaneous tissue disorders	Common	Rash (including dermatitis)
	Uncommon	Increased tendency to bruise, alopecia, dry skin
Musculoskeletal, connective tissue and bone disorders	Uncommon	Arthralgia, pain in extremity
Reproductive system and breast disorders	Uncommon	Amenorrhoea
	Common	Fatigue, asthenia

General disorders and administration site conditions	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 12 months, infections at least possibly related to treatment were reported in 23,2 % of ORENCIA-treated patients and 19,5 % of placebo patients.

Serious infections at least possibly related to treatment were reported in 1,8 % of ORENCIA-treated patients and 1,0 % of placebo patients.

The most frequent (0,1 - 0,3 %) serious infections at least possibly related to treatment reported with ORENCIA were pneumonia, cellulitis, localised infection, urinary tract infection, bronchitis, diverticulitis, acute pyelonephritis, sinusitis and urosepsis.

Malignancies

In placebo-controlled clinical trials with durations of up to 12 months, malignancies were reported in 1,4 % of ORENCIA-treated patients observed during 1 687 patient-years, and in 1,1 % of placebo-treated patients observed during 794 patient-years.

In double-blind and open-label clinical trials in 4 149 patients treated with ORENCIA during 11 658 patient-years (of which over 1 000 were treated with ORENCIA for over 5 years), the incidence rate of malignancy was 1,41 per 100 patient-years, and the annualised incidence rate remained stable.

The incidence rates per 100 patient-years were 0,74 for non-melanomatous skin cancer, 0,57 for solid malignancies and 0,13 for haematologic malignancies. The most frequently reported solid organ cancer was lung cancer (0,15 per 100 patient-years), and the most common haematologic malignancy was lymphoma (0,07 per 100 patient-years).

The incidence rate did not increase for malignancies overall, by major type (non-melanomatous skin cancer, solid tumours, and haematologic malignancies), or for individual tumour types in the double-blind and open-label period compared to the double-blind experience.

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 %]).

Auto-immune processes

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

Injection site reactions

The overall frequency of injection site reactions was 2,6 % (19/736) in patients using ORENCIA 125 mg solution for subcutaneous injection.

Immunogenicity

Across seven studies in rheumatoid arthritis patients treated for up to 8 years with subcutaneous or intravenous administration of ORENCIA, 4,8 % (187/3877) developed anti-abatacept antibodies while on treatment. Samples from 22 of 48 of these patients with binding activity to CTLA-4 showed significant neutralising activity.

A subsequent study compared the immunogenicity to ORENCIA following subcutaneous vs intravenous administration. The overall immunogenicity frequency to ORENCIA was 1,1 % (8/725) and 2,3 % (16/710) for the subcutaneous and intravenous groups, respectively. These rates are consistent with previous experience, and there was no effect of immunogenicity on pharmacokinetics, safety or efficacy.

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 323 patients 65 years of age and older, including 53 patients 75 years and older, received ORENCIA in clinical studies.

Similar efficacy was observed in these patients and younger patients.

The relative frequency of serious infection among ORENCIA-treated patients age 65 and over (18/323 (5,6 %) ORENCIA vs. 4/148 (2,7 %) placebo) was higher than for those under age 65 (40/1 632 (2,5 %) ORENCIA vs. 15/841 (1,8 %) placebo). The relative frequency of malignancy among ORENCIA-treated patients age 65 and over (18/323 (5,6 %) ORENCIA vs. 4/148 (2,7 %) placebo) was higher than for those under age 65 (9/1 632 (0,6 %) ORENCIA vs. 7/841 (0,8 %) placebo). Among patients aged 65 and over, non-melanoma skin cancers accounted for 11 of the 18 malignancy cases in ORENCIA-treated patients, and all 4 of the placebo cases.

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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.

IDENTIFICATION

ORENCIA 125 mg solution for subcutaneous injection is supplied as a sterile, preservative-free, ready-to-use solution for subcutaneous injection.

The solution for injection for subcutaneous administration is a clear, colourless to pale yellow, slightly opalescent solution, essentially free of particulate matter on visual inspection, with a pH of 6,8 to 7,4.

PRESENTATION

ORENCIA solution for subcutaneous injection is supplied as a sterile, preservative-free, ready-to-use solution for subcutaneous injection. The ORENCIA solution for subcutaneous injection is supplied either:

1. in a single-dose disposable prefilled glass syringe with a passive needle safety guard and flange extenders, or
2. in a single-dose disposable pre-filled glass syringe with flange extenders.

The Type I glass syringe has a coated stopper and fixed stainless steel needle (5 bevel, 29-gauge thin wall, ½-inch needle) covered with a rigid needle shield. A sufficient excess of abatacept is incorporated into each syringe to account for needle-syringe losses so that 1,0 ml of solution containing 125 mg abatacept can be dispensed for subcutaneous injection.

Both presentations are packed in cartons containing four pre-filled syringes.

STORAGE INSTRUCTIONS

ORENCIA solution for subcutaneous injection: pre-filled syringes must be protected from light by storing in the original package until time of use. ORENCIA solution for subcutaneous injection must be refrigerated at 2 °C to 8 °C. Do not freeze the pre-filled syringes.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

47/3.1/0467

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