Enerceptan®
Etanercept

25 mg/0.5 ml
50 mg/ml

Solution for Injection in prefilled syringe. Subcutaneous route of administration.

Prescription Only MADE IN ARGENTINA

FORMULA

Each Enerceptan® 25 mg prefilled syringe contains: Etanercept 25 mg and excipients: Sucrose, Sodium chloride, L-arginine hydrochloride, Monobasic sodium phosphate, Dibasic sodium phosphate, Water for injection q.s. 0.5 ml.
Each Enerceptan® 50 mg prefilled syringe contains: Etanercept 50 mg and excipients: Sucrose, Sodium chloride, L-arginine hydrochloride, Monobasic sodium phosphate, Dibasic sodium phosphate, Water for injection q.s. 1.0 ml.

PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe. Subcutaneous route of administration.

CLINICAL DATA

Therapeutic indications

Etanercept is a tumour necrosis factor alpha inhibitor used in:

Rheumatoid arthritis
Etanercept in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to disease-modifying antirheumatic drugs, including methotrexate (unless contraindicated), has been inadequate.
Etanercept can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.
Etanercept is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Juvenile idiopathic arthritis
Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.
Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.
Treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.

Psoriatic arthritis
Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug therapy has been inadequate.

Axial spondyloarthritis. Ankylosing spondylitis (AS)
Treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Non-radiographic axial spondyloarthritis
Treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation, who have had an inadequate response to nonsteroidal anti-inflammatory drugs (NSAIDs).

Plaque psoriasis
Treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy, including ciclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA).

Paediatric plaque psoriasis
Treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

Posology and method of administration

The treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, plaque psoriasis or paediatric plaque psoriasis.

Rheumatoid arthritis
25 mg administered twice weekly is the recommended dose.
Alternatively, 50 mg administered once weekly has been shown to be safe and effective.

Psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis
The recommended dose is 25 mg administered twice weekly, or 50 mg administered once weekly.

For all of the above indications, available data suggest that a clinical response is
usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

Plaque psoriasis
The recommended dose is 25 mg administered twice weekly or 50 mg administered once weekly. Alternatively, 50 mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25 mg twice weekly or 50 mg once weekly. Treatment should continue until remission is achieved, for up to 24 weeks. Continuous therapy beyond 24 weeks may be appropriate for some adult patients. Treatment should be discontinued in patients who show no response after 12 weeks. If re-treatment is indicated, the same guidance on treatment duration should be followed. The dose should be 25 mg twice weekly or 50 mg once weekly.

Special populations
Renal and hepatic impairment: No dose adjustment is required.
Elderly: No dose adjustment is required. The dosage and administration are the same as for adults 18-64 years of age.
Paediatric population: The safety and efficacy of enerceptan in children aged less than 2 years has not been established.

Juvenile idiopathic arthritis
The recommended dose is 0.4 mg/kg (up to a maximum of 25 mg per dose), given twice weekly as a subcutaneous injection with an interval of 3-4 days between doses or 0.8 mg/kg (up to a maximum of 50 mg per dose) given once weekly. Discontinuation of treatment should be considered in patients who show no response after 4 months.
No formal clinical trials have been conducted in children aged 2 to 3 years.
However, limited safety data from a patient registry suggest that the safety profile in children from 2 to 3 years of age is similar to that seen in adults and children aged 4 years and older, when dosed every week with 0.8 mg/kg subcutaneously.
There is generally no applicable use of Enerceptan® in children aged below 2 years in the indication juvenile idiopathic arthritis.

Paediatric plaque psoriasis (age 6 years and above)
The recommended dose is 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly for up to 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks.
If re-treatment is indicated, the above guidance on treatment duration should be followed. The dose should be 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly.
There is generally no applicable use of Enerceptan® in children aged below 6 years in the indication plaque psoriasis.

METHOD OF ADMINISTRATION

Subcutaneously in arm, abdomen, or thigh. Do not apply each injection in the same place.

CONTRAINDICTIONS

- Hypersensitivity to the active substance or to any of the excipients.
- Sepsis or risk of sepsis.
- Treatment with Enerceptan® should not be initiated in patients with active infections, including chronic or localised infections.

WARNINGS AND PRECAUTIONS

Infeccions
Serious infections, sepsis, tuberculosis, and opportunistic infections, including invasive fungal infections, listeriosis and legionellosis, have been reported with the use of etanercept. These infections were due to bacteria, mycobacteria, fungi, viruses and parasites (including protozoa).
Patients who develop a new infection while undergoing treatment with etanercept should be monitored closely. Administration of etanercept should be discontinued if a patient develops a serious infection. The safety and efficacy of etanercept in patients with chronic infections have not been evaluated. Physicians should exercise caution when considering the use of etanercept in patients with a history of recurring or chronic infections.

Tuberculosis
Before starting treatment with Enerceptan®, all patients must be evaluated for both active and inactive ('latent') tuberculosis. If active tuberculosis is diagnosed, Enerceptan® therapy must not be initiated. If inactive ('latent') tuberculosis is diagnosed, treatment for latent tuberculosis must be started with anti-tuberculosis therapy before the initiation of Enerceptan®, and in accordance with local recommendations. In this situation, the benefit/risk balance of Enerceptan® therapy should be very carefully considered.
All patients should be informed to seek medical advice if signs/symptoms suggestive of tuberculosis (e.g., persistent cough, wasting/weight loss, low-grade fever) appear during or after treatment.

Hepatitis B reactivation
Reactivation of hepatitis B in patients who were previously infected with the hepatitis B virus (HBV) and had received concomitant TNF-antagonists, including etanercept, has been reported.
Patients should be tested for HBV infection before initiating treatment with Enerceptan®.
For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Caution should be exercised when administering Enerceptan® in patients previously infected with HBV. These patients should be monitored for signs and symptoms of active HBV infection throughout therapy and for several weeks following termination of therapy. In patients who develop HBV infection, Enerceptan® should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Worsening of hepatitis C
There have been reports of worsening of hepatitis C in patients receiving etanercept. etanercept should be used with caution in patients with a history of hepatitis C.

Concurrent treatment with anakinra
Serious infections and neutropenia may occur in patients receiving etanercept in combination with anakinra. This combination is not recommended.

Concurrent treatment with abatacept
The appearance of some serious adverse effects in concomitant use of abatacept and etanercept is noted. This combination is not recommended.

Allergic reactions
Allergic reactions associated with etanercept administration have been reported (including angioedema and urticaria). If any serious allergic or anaphylactic reaction occurs, Enerceptan® therapy should be discontinued immediately and appropriate therapy initiated.

Immunosuppression
The possibility exists for TNF-antagonists, including etanercept, to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses.
Patients with a significant exposure to varicella virus should temporarily discontinue etanercept therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.
The safety and efficacy of etanercept in patients with immunosuppression have not been evaluated.

Malignancies and lymphoproliferative disorders
Solid and haematopoietic malignancies (excluding skin cancers)
Reports of various malignancies (including breast and lung carcinoma and lymphoma) have been received in the postmarketing period. In the postmarketing setting, cases of leukaemia have been reported in patients treated with TNF-antagonists.
Based on current knowledge, a possible risk for the development of lymphomas, leukaemia or other haematopoietic or solid malignancies in patients treated with a TNF-antagonist cannot be excluded. Caution should be exercised when considering TNF-antagonist therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.
A risk for the development of malignancies in children and adolescents treated with TNF-antagonists cannot be excluded.

Skin cancers
Melanoma and non-melanoma skin cancer (NMSC) have been reported in patients treated with TNF-antagonists, including etanercept. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Vaccinations
Live vaccines should not be given concurrently with etanercept. No data are available on the secondary transmission of infection by live vaccines in patients receiving etanercept.
Vaccination according to the planned vaccination schedules is recommended in paediatric patients before starting treatment with etanercept.

Autoantibody formation
Treatment with etanercept may result in the formation of autoimmune antibodies.

Haematologic reactions
Caution should be exercised in patients being treated with etanercept who have a previous history of blood dyscrasias. All patients and parents/caregivers should be advised that if the patient develops signs and symptoms suggestive of blood dyscrasias or infections (e.g., persistent fever, sore throat, bruising, bleeding, paleness) whilst on etanercept, they should seek immediate medical advice. If blood dyscrasias are confirmed, etanercept should be discontinued.

Neurological disorders
There have been rare reports of CNS demyelinating disorders in patients treated with etanercept. Additionally, there have been rare reports of peripheral demyelinating polyneuropathies. A careful risk/benefit evaluation, including a

neurologic assessment, is recommended when prescribing etanercept to patients with pre-existing or recent onset of demyelinating disease, or to those who are considered to have an increased risk of developing demyelinating disease.

Combination therapy
The combination of etanercept and methotrexate did not result in unexpected safety findings. The long-term safety of etanercept in combination with other disease-modifying antirheumatic drugs (DMARD) has not been established. The use of etanercept in combination with other systemic therapies or phototherapy for the treatment of psoriasis has not been studied.

Renal and hepatic impairment
Based on pharmacokinetic, no dose adjustment is needed in patients with renal or hepatic impairment; clinical experience in such patients is limited.

Congestive heart failure (CHF)
It is advised over the possibility of worsening of CHF, with and without identifiable precipitating factors, in patients taking etanercept. There have also been rare reports of new onset CHF, including CHF in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age.

Alcoholic hepatitis
Etanercept should not be used in patients for the treatment of alcoholic hepatitis. Physicians should use caution when using etanercept in patients who also have moderate to severe alcoholic hepatitis.

Wegener's granulomatosis
It has not shown etanercept to be an effective treatment for Wegener's granulomatosis. Etanercept is not recommended for the treatment of granulomatosis.

Hypoglycaemia in patients treated for diabetes
There have been reports of hypoglycaemia following initiation of etanercept in patients receiving medication for diabetes, necessitating a reduction in anti-diabetic medication in some of these patients.

Special populations
Elderly: Caution should be exercised when treating the elderly and particular attention paid with respect to occurrence of infections.
Paediatric population. Vaccinations: It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating the treament.

INTERACTIONS

Interactions could arise from concomitant use of etanercept with a human interleukin-1 receptor antagonist such as anakinra. Serious infections and neutropenia could develop with this interaction.
In the administration of etanercept and a selective co-stimulation modulator that inhibits co-stimulation of T cells such as abatacept, the incidence of serious adverse reactions could increase, without showing benefit. This combination is not recommended.
The co-administration of sulfasalazine and etanercept cause a decrease in the white blood cell count.
Drugs that have not shown interaction with etanercept are digoxin, warfarin, methotrexate, glucocorticoids, analgesics, salicylates (except sulfasalazine described above), and NSAIDs.

FERTILITY, PREGNANCY AND LACTATION

Women of childbearing potential
Women of childbearing potential should consider the use of appropriate contraception to avoid becoming pregnant during etanercept therapy and for three weeks after discontinuation of therapy.

Pregnancy
The use of Enerceptan® during pregnancy is not recommended. Preclinical and Clinical studies also showed no increased risks of minor birth defects, preterm birth, stillbirth.
Etanercept should only be used during pregnancy if clearly needed and after an exhaustive evaluation.
Etanercept crosses the placenta and has been detected in the serum of infants born to female patients treated during pregnancy. The clinical impact of this is unknown, however, infants may be at increased risk of infection. Administration of live vaccines to infants for 16 weeks after the mother's last dose of etanercept is generally not recommended.

Breast-feeding
Etanercept has been reported to be excreted in human milk following subcutaneous administration. A decision must be made whether to discontinue breast-feeding or to discontinue etanercept therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
Data about peri- and postnatal toxicity of etanercept and of effects of etanercept

on fertility and general reproductive performance are not available.

Effects on the ability to operate or use machinery

Etanercept has no or negligible influence on the ability to drive and use machines.

ADVERSE REACTIONS

Summary of the safety profile
The most commonly reported adverse reactions are injection site reactions (such as pain, swelling, itching, reddening and bleeding at the puncture site), infections (such as upper respiratory infections, bronchitis, bladder infections and skin infections), headache, allergic reactions, development of autoantibodies, itching, and fever.
Serious adverse reactions have also been reported for etanercept. TNF-antagonists, such as etanercept, affect the immune system and their use may affect the body's defenses against infection and cancer. Serious infections affect fewer than 1 in 100 patients treated with etanercept. Reports have included fatal and life-threatening infections and sepsis. Various malignancies have also been reported with use of etanercept, including cancers of the breast, lung, skin and lymph glands (lymphoma).
Serious haematological, neurological and autoimmune reactions have also been reported. These include rare reports of pancytopenia and very rare reports of aplastic anaemia.
Central and peripheral demyelinating events have been seen rarely and very rarely, respectively, with etanercept use. There have been rare reports of lupus, lupus-related conditions, and vasculitis.

Tabulated list of adverse reactions
The following list of adverse reactions is based on experience from clinical trials and on postmarketing experience.

Within the organ system classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), 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); not known (cannot be estimated from the available data).

System Organ Class	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	Not Known (Cannot be Estimated from Available Data)
Infections and infestations	Infection (including upper respiratory tract infection, bronchitis, cystitis, skin infection)		Serious infections (including pneumonia, cellulitis, arthritis bacterial, sepsis and parasitic infection)	Tuberculosis, opportunistic infection (including invasive fungal, protozoal, bacterial, atypical mycobacterial, viral infections, and Legionella)		Hepatitis B reactivation, listeria
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Non-melanoma skin cancers	Malignant melanoma, lymphoma, leukaemia		Merkel cell carcinoma, Kaposi's sarcoma
Blood and lymphatic system disorders			Thrombocytopenia, anaemia, leukopenia, neutropenia	Pancytopenia	Aplastic anaemia	Histocytosis haematophagic (macrophage activation syndrome)
Immune system disorders		Allergic reactions, autoantibody formation	Vasculitis (including antineutrophilic cytoplasmic antibody positive vasculitis)	Serious allergic/anaphylactic reactions (including angioedema, bronchospasm), sarcoidosis		Worsening of symptoms of dermatomyositis
Nervous system disorders	Headache			CNS demyelinating events suggestive of multiple sclerosis or localised demyelinating conditions, such as optic neuritis and transverse myelitis ; peripheral demyelinating events including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy, seizure		
Eye disorders			Uveitis, scleritis			
Cardiac disorders			Worsening of cardiac failure congestive	New onset cardiac failure congestive		
Respiratory, thoracic, and mediastinal disorders				Interstitial lung disease (including pneumonitis and pulmonary fibrosis		

Gastrointestinal disorders			Inflammatory bowel disease			
Hepatobiliary disorders			Elevated liver enzymes	Autoimmune hepatitis		
Skin and Subcutaneous tissue disorders		Pruritus, rash	Angioedema, psoriasis (including new onset or worsening and pustular, primarily palms and soles), urticaria, psoriasiform rash	Stevens-Johnson syndrome, cutaneous vasculitis (including hypersensitivity vasculitis), erythema multiforme, lichenoid reactions	Toxic Epidermal necrolysis	
Musculoskeletal and connective tissue disorders				Cutaneous lupus erythematosus, subacute cutaneous lupus erythematosus, lupus-like syndrome		
General disorders and administration site conditions	Injection site reactions (including bleeding, bruising, erythema/itching, pain, swelling)	Pyrexia				

DESCRIPTION OF SELECTED ADVERSE REACTIONS

Malignancies and lymphoproliferative disorders
One hundred and twenty-nine (129) new malignancies of various types were observed in 4,114 rheumatoid arthritis patients treated in clinical trials with etanercept for up to approximately 6 years, including 231 patients treated with etanercept in combination with methotrexate in the 2-year active-controlled study. The observed rates and incidences in these clinical trials were similar to those expected for the population studied. A total of 2 malignancies were reported in clinical studies of approximately 2 years duration involving 240 etanercept treated psoriatic arthritis patients. In clinical studies conducted for more than 2 years with 351 ankylosing spondylitis patients, 6 malignancies were reported in etanercept treated patients. In a group of 2,711 plaque psoriasis patients treated with etanercept in double-blind and open-label studies of up to 2.5 years, 30 malignancies and 43 nonmelanoma skin cancers were reported. In a group of 7,416 patients treated with etanercept in rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and psoriasis clinical trials, 18 lymphomas were reported.
Reports of various malignancies (including breast and lung carcinoma and lymphoma) have also been received in the postmarketing period.

Injection site reactions
Compared to placebo, patients with rheumatic diseases treated with etanercept had a significantly higher incidence of injection site reactions (36% vs. 9%). Injection site reactions usually occurred in the first month. Mean duration was approximately 3 to 5 days. No treatment was given for the majority of injection site reactions in the etanercept treatment groups, and the majority of patients who were given treatment received topical preparations, such as corticosteroids, or oral antihistamines. Additionally, some patients developed recall injection site reactions characterised by a skin reaction at the most recent site of injection, along with the simultaneous appearance of injection site reactions at previous injection sites. These reactions were generally transient and did not recur with treatment. In controlled trials in patients with plaque psoriasis, approximately 13.6% of patients treated with etanercept developed injection site reactions compared with 3.4% of placebo-treated patients during the first 12 weeks of treatment.

Serious infections
In placebo-controlled trials, no increase in the incidence of serious infections (fatal, life-threatening, or requiring hospitalisation or intravenous antibiotics) was observed. Serious infections occurred in 6.3% of rheumatoid arthritis patients treated with etanercept for up to 48 months. These included abscess (at various sites), bacteraemia, bronchitis, bursitis, cellulitis, cholecystitis, diarrhoea, diverticulitis, endocarditis (suspected), gastroenteritis, hepatitis B, herpes zoster, leg ulcer, mouth infection, osteomyelitis, otitis, peritonitis, pneumonia, pyelonephritis, sepsis, septic arthritis, sinusitis, skin infection, skin ulcer, urinary tract infection, vasculitis, and wound infection. In the 2-year active-controlled study where patients were treated with either etanercept alone, methotrexate alone or etanercept in combination with methotrexate, the rates of serious infections were similar among the treatment groups. However, it cannot be excluded that the combination of etanercept with methotrexate could be associated with an increase in the rate of infections.
There were no differences in rates of infection among patients treated with etanercept and those treated with placebo for plaque psoriasis in placebo-controlled trials of up to 24 weeks duration. Serious infections experienced by etanercept -treated patients included cellulitis, gastroenteritis, pneumonia, cholecystitis, osteomyelitis, gastritis, appendicitis, Streptococcal fasciitis, myositis, septic shock, diverticulitis and abscess.
In the double-blind and open-label psoriatic arthritis trials, 1 patient reported a serious infection (pneumonia).
Serious and fatal infections have been reported during use of etanercept ; reported pathogens include bacteria, mycobacteria (including tuberculosis), viruses and fungi.
Some have occurred within a few weeks after initiating treatment with etanercept in patients who have underlying conditions (e.g., diabetes, congestive heart failure, history of active or chronic infections). The treatment with etanercept may increase mortality in patients with established sepsis.
Opportunistic infections have been reported in association with etanercept, including invasive fungal, parasitic (including protozoal), viral (including herpes zoster), bacterial (including Listeria and Legionella), and atypical mycobacterial

infections. In a pooled data set of clinical trials, the overall incidence of opportunistic infections was 0.09% for the 15,402 subjects who received etanercept. The exposure-adjusted rate was 0.06 events per 100 patient-years. In postmarketing experience, approximately half of all of the case reports of opportunistic infections worldwide were invasive fungal infections.
The most commonly reported invasive fungal infections included Candida, Pneumocystis, Aspergillus, and Histoplasma. Invasive fungal infections accounted for more than half of the fatalities amongst patients who developed opportunistic infections. The majority of the reports with a fatal outcome were in patients with Pneumocystis pneumonia, unspecified systemic fungal infections, and aspergillosis.

Autoantibodies
Adult patients had serum samples tested for autoantibodies at multiple timepoints.
Of the rheumatoid arthritis patients evaluated for antinuclear antibodies (ANA), the percentage of patients who developed new positive ANA (≥1:40) was higher in patients treated with etanercept (11%) than in placebo-treated patients (5%). The percentage of patients who developed new positive anti-double-stranded DNA antibodies was also higher by radioimmunoassay (15% of patients treated with etanercept compared to 4% of placebo-treated patients) and by Crithidia luciliae assay (3% of patients treated with etanercept compared to none of placebo-treated patients). The proportion of patients treated with etanercept who developed anticardiolipin antibodies was similarly increased compared to placebo-treated patients. The impact of long-term treatment with etanercept on the development of autoimmune diseases is unknown.
There have been rare reports of patients, including rheumatoid factor positive patients, who have developed other autoantibodies in conjunction with a lupus-like syndrome or rashes that are compatible with subacute cutaneous lupus or discoid lupus by clinical presentation and biopsy.

Pancytopenia and aplastic anaemia
There have been postmarketing reports of pancytopenia and aplastic anaemia, some of which had fatal outcomes.

Interstitial lung disease
In controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of interstitial lung disease in patients receiving etanercept without concomitant methotrexate was 0.06% (frequency rare). In the controlled clinical trials that allowed concomitant treatment with Etanercept and methotrexate, the frequency (incidence proportion) of interstitial lung disease was 0.47% (frequency uncommon). There have been postmarketing reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes.

Concurrent treatment with anakinra
In studies when adult patients received concurrent treatment with etanercept plus
anakinra, a higher rate of serious infections compared to etanercept alone was observed.

Elevated liver enzymes
In the double-blind periods of controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of adverse events of elevated liver enzymes in patients receiving etanercept without concomitant methotrexate was 0.54% (frequency uncommon). In the double-blind periods of controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of adverse events of elevated liver enzymes was 4.18% (frequency common).

Autoimmune hepatitis
In controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of autoimmune hepatitis in patients receiving etanercept without concomitant methotrexate was 0.02% (frequency rare). In the controlled clinical trials that allowed concomitant treatment with Etanercept and methotrexate, the frequency (incidence proportion) of autoimmune hepatitis was 0.24% (frequency uncommon).

PAEDIATRIC POPULATION
Undesirable effects in paediatric patients with juvenile idiopathic arthritis.
In general, the adverse events in paediatric patients with juvenile idiopathic arthritis were similar in frequency and type to those seen in adult patients. Differences from adults and other special considerations are discussed in the following paragraphs.
The types of infections seen in clinical trials in juvenile idiopathic arthritis patients aged 2 to 18 years were generally mild to moderate and consistent with those commonly seen in outpatient paediatric populations. Severe adverse events reported included varicella with signs and symptoms of aseptic meningitis, which resolved without sequelae, appendicitis, gastroenteritis, depression/personality disorder, cutaneous ulcer, oesophagitis/gastritis, group.
A streptococcal septic shock, type I diabetes mellitus, and soft tissue and post-operative wound infection.
In one study in children with juvenile idiopathic arthritis aged 4 to 17 years, 43 of 69 (62%) children experienced an infection while receiving etanercept during 3

months of the study (part 1, open-label), and the frequency and severity of infections was similar in 58 patients completing 12 months of open-label extension therapy. The types and proportion of adverse events in juvenile idiopathic arthritis patients were similar to those seen in trials of etanercept in adult patients with rheumatoid arthritis, and the majority were mild. Several adverse events were reported more commonly in 69 juvenile idiopathic arthritis patients receiving 3 months of etanercept compared to the 349 adult rheumatoid arthritis patients.
These included headache (19% of patients, 1.7 events per patient year), nausea (9%, 1.0 event per patient year), abdominal pain (19%, 0.74 events per patient year), and vomiting (13%, 0.74 events per patient year).
There were 4 reports of macrophage activation syndrome in juvenile idiopathic arthritis clinical trials.
Undesirable effects in paediatric patients with plaque psoriasis
In a 48-week study in 211 children aged 4 to 17 years with paediatric plaque psoriasis, the adverse events reported were similar to those seen in previous studies in adults with plaque psoriasis.

OVERDOSAGE
No dose-limiting toxicities were observed during clinical trials of rheumatoid arthritis patients. The highest dose level evaluated has been an intravenous loading dose of 32 mg/m2 followed by subcutaneous doses of 16 mg/m2 administered twice weekly. One rheumatoid arthritis patient mistakenly self-administered 62 mg etanercept subcutaneously twice weekly for 3 weeks without experiencing undesirable effects. There is no known antidote to etanercept.
In the event of overdose, go immediately to the closest hospital or contact the following toxicology centers:
In Argentina:
Hospital de Pediatría Ricardo Gutiérrez: (011) 4962-6666/2247/ 0800-444- 8694
Centro Nacional de Intoxicaciones Hospital A. Posadas: (011) 4654-6648/4658-7777/0800-333-0160.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamics properties
Pharmacotherapeutic group: Immunosuppresant agent, antineoplastic and immunomodulator agent - Tumor necrosis factor inhibitor.
ATC Code: L04AB01.
Etanercept is a dimeric fusion protein consisting of tumor necrosis factor receptor p75 bound to the Fc portion of the human immunoglobulin IgG1. This protein was obtained by a recombinant DNA technology from a hamster ovarian cell (CHO) culture. The Fc portion consists of CH_2 and CH_3 domains, but not the CH_1 domain, and the hinge region.
Etanercept contains 934 aminoacids, weighs about 150 kDa and has specific activity of 1.4 x 10^6 units/mg.
This protein is intended to bind to TNF, thus blocking its interaction with the surface cell receptors. Therefore, it directly intervenes with the inflammatory and immune responses, particularly, in the inflammatory process of rheumatoid arthritis, juvenile idiopathic rheumatoid arthritis and ankylosing spondylitis.
Etanercept can modulate the biologic responses controlled by other TNF-induced or regulated molecules, e.g. citokines, adhesion molecules or proteinases.

Pharmacokinetics properties
Maximum concentration is reached 48 hours after the administration and the bioavailability after the use achieves 76%.
The maximum concentration reached after the administration of 25 mg would be 1.65 ± 0.66 µg/ml, with no evidence of clearance saturation for this dose.
The distribution volume for the 25 mg dose is estimated to be 13.9 ± 9.4 liters.
Both etanercept absorption and elimination are slow, with an average life of 80 hours.
For patients with these diseases, elimination clearance is about 175 ± 116 ml/h.
The need for dose adjustment in patients suffering from liver failure receiving Etanercept has not been established.
A single 50 mg/ml dose is expected to be equal to two consecutive 25 mg/ml doses.

PRECLINICAL SAFETY DATA
In the toxicological studies with etanercept, no dose-limiting or target organ toxicity was evident. Etanercept was considered to be non-genotoxic from a battery of *in vitro* and *in vivo* studies. Carcinogenicity studies, and standard assessments of fertility and postnatal toxicity, were not performed with etanercept due to the development of neutralising antibodies in rodents.
Etanercept does not induce fatality or noticeable toxicity signs in mice or rats after a single subcutaneous 2000 mg/kg dose or after a single intravenous 1000 mg/kg dose.
There is no evidence of dose-limiting or target-organ toxicity in the cynomolgus monkey after subcutaneous administration twice a week during 4 or 26 consecutive weeks at a (15 mg/kg) dose resulting in an area under the curve (AUC) based on drug serum concentrations 27 times greater than those obtained in humans at the 25 mg recommended dose.

PHARMACEUTICAL INFORMATION
Incompatibilities
Incompatibilities have not been studied, but concomitant administration with other medication is not recommended.

STORAGE CONDITION
It should be stored between 2ºC to 8ºC. Keep in original packaging. Do not freeze.

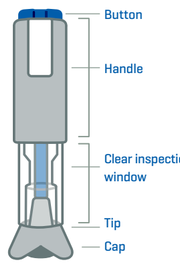
Special precautions of disposal and other handling
The solution for Injection in prefilled syringes is ready to be used. It can also be administered with a proper auto-injector. The syringe and its contents are intended for a single use. Use only particle-free solutions without visible signs of damage.

INSTRUCTIONS FOR USE
How to administer the product
Enerceptan® must be injected subcutaneously.
If possible, the first injection should be administered under the supervision of a duly qualified professional. Since Enerceptan® is packaged in prefilled syringes for subcutaneous administration, you or a family member or a friend can safely administer the medication at home.

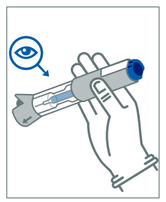
For Enerceptan® administration, read the following instructions:
Subcutaneous administration (under the skin)

PREFILLED SYRINGE WITHOUT AUTOINJECTOR
1. Read the instructions and administer Enerceptan® every day at the same time.
2. Wash your hands and sanitize the area where you will place the items.
3. Gather all the items you will need: full container with prefilled Enerceptan® syringe + cotton + alcohol + plastic sharp container.
4. Check that the final solution is clear and has no particles. **Do not shake the syringe.**
5. Remove air bubbles that may be in the syringe by gently tapping it while it is in upright position. Gently push the plunger until the air bubbles disappear.
6. Inject the solution immediately with your physician or nurse's aide or as per instruction.
Injection sites: abdomen, front of the thigh. Avoid irritation by choosing a different site for each injection and rotate the injection sites.
7. Sanitize the skin by applying circular moves with an alcohol cotton swab.
8. Remove the protecting cap from the syringe. Do not touch the needle and do not let the syringe come in contact with any surface.
9. Fold the skin in the injection site by firmly grabbing the skin with the thumb and the forefinger with one hand. With the other hand, inject the needle at a 45° to 90°angle.
10. Gently push the plunger until all the liquid is introduced. Do not directly inject into a vein.

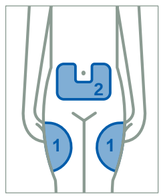
PREFILLED SYRINGE WITH AUTOINJECTOR
Components of autoinjector



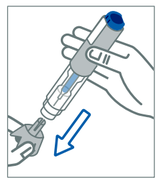
Step 1: Supplies needed for injection administration
a. One BDPHYSIOJECT prefilled autoinjector
b. Cotton or gauze impregnated with alcohol
c. A sharps disposal container to throw the autoinjector away after use



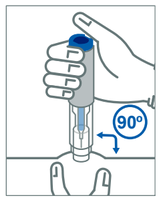
Step 2: How to prepare for injection administration
a. Take the autoinjector out of the refrigerator, wait for approximately 15-30 minutes to allow the solution in the autoinjector to reach room temperature.
b. Wash your hands thoroughly with soap and warm water.
c. Grab the autoinjector by the handle and check that it is in good condition before use.
Important – If you notice that the autoinjector may be damaged or has fallen down, do not use it and throw it away in the sharps disposal container. Use another autoinjector. Contact your doctor, pharmacist or nurse for further instructions.
d. Place the autoinjector on a flat, stable surface.



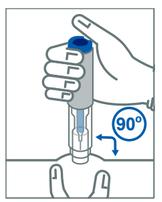
Step 3: Choosing the injection site
a. The recommended injection sites are the upper thighs (area 1) and the abdomen (area 2), except for the area around the navel.
b. Choose a different site for each injection. Do not inject into areas where the skin is red, bruised, injured or abnormal in any way. Your doctor may recommend another injection site.

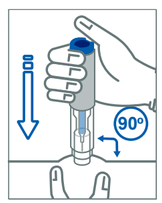


Step 4: Giving your injection
a. Clean the injection site using gauze or cotton impregnated with alcohol in a circular motion and allow your skin to dry.
b. Grab the autoinjector by the handle. Remove the cap with the other hand and throw it away.
Important – Remove the cap just before giving your injection.

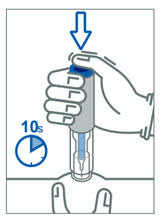


c. Softly pinch a considerable area of clean skin using the other hand,creating a fold on which to place the end of the autoinjector **(do not release the skin fold until the end of the injection)**. Place the open end of the autoinjector at a 90° angle on the skin fold.

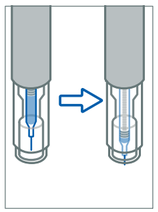




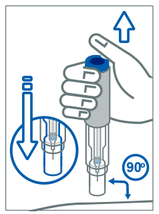
d. Push the autoinjector down until the stop point is felt. By pushing up to this point, the button will unlock.



e. While holding the autoinjector firmly against the skin, press the button with your thumb or index finger (you will hear a click indicating that the injection has started). Hold the autoinjector in place. The injection will last approximately 10 seconds.
Important – If the injection does not start: release the button, make sure that the autoinjector is firmly pressed against the skin until you feel that the autoinjector has stopped, and press the button harder.



f. Check the injection by looking through the clear inspection window to make sure that the dose has been fully injected.When the movement stops, the injection is complete.Keep pressing the autoinjector against the skin a few more seconds.
Important – To avoid incomplete injection, do not remove the autoinjector from the skin before the end of the injection.



g. Lift the autoinjector from the injection site and release the fold of skin. The needle cover will automatically extend to cover the needle. Then, it will lock and the needle will be covered.
h. Before disposing of the autoinjector,make sure that there is no liquid left in the syringe by looking through the lower part of the clear inspection window. If the medicine has not been injected completely, contact your doctor.
Important – To avoid injuries, do not touch the needle.

Step 5: How to safely dispose of the BD Physioject autoinjector.
a. Dispose of the used autoinjector in the sharps disposal container as instructed by your doctor, nurse or pharmacist.
Important – Always keep the sharps disposal container out of the reach and sight of children.
Important:
• Always keep the autoinjector out of the reach and sight of children.
• Store the autoinjector away from direct sunlight.
• If someone is injured by the needle, contact your doctor.
• Subcutaneous injections may occasionally cause transient pain and/or minor bruises in the injection site.
• **Remember, "Do not release the skin fold until the end of the injection".**
• If you have any questions, contact your doctor, nurse or pharmacist.
• The solution in the prefilled syringe of the autoinjector is ready to use.

SUSPECTED ADVERSE REACTIONS
If you believe you may be experiencing an adverse reaction, you may report it to GEMABIOTECH S.A.U. Call the toll-free line 0-800-888-0009 or send an email to the Pharmacovigilance Unit: farmacovigilancia@gemabiotech.com.
Moreover, you can report any problems with the medicinal product by filling the form available at the ANMAT website: http://www.anmat.gov.ar/farmacovigilancia/Notificar.asp or calling at 0800-333-1234

HOW SUPPLIED
Type I glass 1 ml syringe, a stainless-steel needle included, which contains 0.5 ml solution to be administered subcutaneously.
Type I glass 1 ml syringe, a stainless-steel needle included, which contains 1 ml solution to be administered subcutaneously.

Enerceptan® 25 mg is available in 1, 2, 4, or 12 prefilled syringes per box.
Enerceptan® 50 mg is available in 1, 2, 4, or 12 prefilled syringes per box.
Enerceptan® 50 mg is available in a box of 4 autoinjectors, containing each autoinjector 1 prefilled syringe of 50 mg.

KEEP THIS AND ALL MEDICATIONS OUT OF REACH OF CHILDREN.
Use only as indicated under medical supervision.
Do not repeat the use of the drug without medical indication.
Do not use this drug if you observe any signs of deterioration.
Do not use this or any other drug after its expiration date.

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Technical Director: Adriana Carey, Pharmacist
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Medicinal Product authorized by the Argentine Ministry of Health
Certificate No. 58792

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