

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

^{PR} **BRENZYS**TM

etanercept

Solution for Injection in a Pre-filled Syringe 50 mg/mL

and

Solution for Injection in a Pre-filled Auto-injector 50 mg/mL

Pharmacopoeial Standard: Professed

Biological Response Modifier

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PR **BRENZYS**TM

etanercept

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medical Ingredients
Subcutaneous injection (SC)	Sterile solution for injection/ 50 mg/mL pre-filled syringe (0.98 mL) and 50 mg/mL auto-injector (0.98 mL)	Not Applicable <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

DESCRIPTION

BRENZYS (etanercept) is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) tumour necrosis factor receptor (TNFR) linked to the Fc portion of human immunoglobulin (IgG1). Etanercept is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system. It consists of 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons.

BRENZYS has been developed as a Subsequent Entry Biologics (SEB) to the reference medicinal product Enbrel[®]. Similarity between BRENZYS and Enbrel[®] (the reference product) was established in accordance with the *Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs)*, for the authorized indications.

INDICATIONS AND CLINICAL USE

Comparability between BRENZYS and the reference product has been established based on comparative chemistry and manufacturing studies, comparative non-clinical studies, a comparative PK study and clinical trials in patients with Rheumatoid Arthritis (RA). An indication for Ankylosing Spondylitis (AS) has been granted on the basis of similarity, between BRENZYS and the reference product, in product quality, mechanism of action, disease pathophysiology, safety profile, dosage regimen and on clinical experience with the reference product.

BRENZYS (etanercept) is indicated for:

- treatment of moderately to severely active rheumatoid arthritis in adults. Treatment is effective in reducing the signs and symptoms of RA, inducing major clinical response,

inhibiting the progression of structural damage, and improving physical function. BRENZYS can be initiated in combination with methotrexate (MTX) in adult patients or used alone.

- reducing signs and symptoms of active ankylosing spondylitis.

Improvement may be seen as early as 1 week after initial administration of etanercept in adults. Attainment of full effect was usually seen by 3 months in both populations and remained durable thereafter with continued treatment with etanercept. Some patients see continuing improvement after 3 months of treatment with etanercept.

After discontinuation of etanercept, symptoms of arthritis generally returned within a month. Reintroduction of treatment with etanercept in adults after discontinuation of up to 18 months resulted in the same magnitudes of response as patients who received etanercept without interruption of therapy based on results of open-label studies.

Geriatrics (> 65 years of age):

Four hundred and eighty RA patients in clinical studies performed with the reference product, Enbrel[®] were age 65 or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Because there is greater sensitivity and predisposition of older individuals to infection, caution should be used in treating the elderly (see WARNINGS AND PRECAUTIONS/Special Populations/Geriatrics).

Pediatrics (< 18 years of age):

BRENZYS is not indicated for use in children less than 18 years of age. Therefore, BRENZYS should not be used for children less than 18 years of age.

CONTRAINDICATIONS

- Patients who are hypersensitive to etanercept or to any of the excipients. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- Patients with, or at risk of, sepsis syndrome, such as immunocompromised and HIV+ patients.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Infections

- **Serious infections leading to hospitalization or death, including sepsis, tuberculosis (TB), invasive fungal and other opportunistic infections, have been observed with the use of TNF blocking agents including etanercept. Cases of TB may be due to reactivation of latent TB infection or to new infection.**
- **Treatment with BRENZYS should not be initiated in patients with active infections including TB, chronic or localized infections. Administration of BRENZYS should be discontinued if a patient develops a serious infection or sepsis.**
- **Physicians also should exercise caution when considering the use of BRENZYS in patients with a history of recurring or latent infections, including TB, or with underlying conditions, which may predispose patients to infections, such as advanced or poorly controlled diabetes.**
- **Before starting treatment with BRENZYS, all patients should be evaluated for both active and inactive ('latent') TB. If inactive ('latent') TB is diagnosed, treatment for latent TB should be started with anti-TB therapy before the initiation of BRENZYS.**
- **Patients should be monitored for the development of signs and symptoms of infection during and after treatment with BRENZYS, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy (see further detail in Serious and Opportunistic Infections section below).**

Malignancies

- **Although BRENZYS is not indicated for use in children less than 18 years of age, lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including etanercept (see further detail in Malignancies/Pediatric Patients section below).**

Serious and Opportunistic Infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic (including protozoal), or other opportunistic pathogens have been reported in patients receiving TNF-blocking agents. Tuberculosis, histoplasmosis, aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, legionellosis, listeriosis, and pneumocystosis have been reported (see ADVERSE REACTIONS/Infections section). Patients have frequently presented with disseminated rather than localized

disease. Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their underlying disease, could predispose them to infections.

Treatment with BRENZYS should not be initiated in patients with an active infection, including clinically important localized infections. The risks and benefits of treatment should be considered prior to initiating therapy in patients:

- With chronic or recurrent infection;
- Who have been exposed to tuberculosis;
- With a history of an opportunistic infection;
- Who have resided or traveled in areas of endemic tuberculosis or mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis;
- With underlying conditions that may predispose them to infection such as advanced or poorly controlled diabetes.

Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving etanercept, including patients who have previously received treatment for latent or active tuberculosis. Patients should be evaluated according to the Canadian Tuberculosis Standards guidelines for tuberculosis risk factors and tested for latent infection prior to initiating BRENZYS and during therapy as appropriate. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immuno-compromised.

If active tuberculosis is diagnosed, BRENZYS therapy should not be initiated. If inactive ('latent') tuberculosis is diagnosed, treatment for latent TB should be started with anti-tuberculosis therapy before the initiation of BRENZYS. In this situation, the benefit/risk balance of BRENZYS therapy should be very carefully considered. Anti-tuberculosis therapy should also be considered prior to initiation of BRENZYS in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Patients should be monitored for the development of signs and symptoms of infection during and after treatment with BRENZYS, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may be falsely negative while on therapy with BRENZYS.

Tuberculosis should be strongly considered in patients who develop a new infection during BRENZYS treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Histoplasmosis and other invasive fungal infections are not consistently recognized in patients taking TNF blockers, including etanercept. This has resulted in delays in appropriate treatment, sometimes resulting in death. For patients who reside or travel

in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. Appropriate empiric antifungal therapy may be initiated while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and taking into account both the risk for severe fungal infection and the risks of antifungal therapy.

BRENZYS should be discontinued if a patient develops a serious infection or sepsis. A patient who develops a new infection during treatment with BRENZYS should be closely monitored, undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and antimicrobial therapy should be initiated, as appropriate.

In post-marketing studies of the reference product, etanercept, in patients with juvenile idiopathic arthritis, for which BRENZYS is not indicated, serious infections have been reported in approximately 3% of patients. Sepsis has also been reported in the post-market setting of etanercept (0.8%).

Neurologic Events

Treatment with TNF blocking agents, including etanercept has been associated with rare cases of new onset or exacerbation of central nervous system disorders, including demyelinating disorders, some presenting with mental status changes and some associated with permanent disability, and with peripheral nervous system demyelinating disorders. Rare cases of transverse myelitis, optic neuritis, and new onset or exacerbation of seizure disorders have been observed in association with etanercept therapy. Guillain-Barré like syndromes have been reported very rarely in postmarketing experience with etanercept therapy. While no clinical trials have been performed evaluating etanercept therapy in patients with multiple sclerosis, other TNF antagonists administered to patients with multiple sclerosis have been associated with increases in disease activity. Prescribers should exercise caution in considering the use of BRENZYS in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders. Development of new, confirmed central nervous system demyelination in patients on BRENZYS warrants consideration of discontinuation of the medication.

Hematologic Events

Rare cases (less than 1 case out of 1000 patients treated) of neutropenia, leukopenia, thrombocytopenia, anemia and pancytopenia (including aplastic anemia), some with fatal outcomes, have been reported in patients treated with etanercept. Cases of pancytopenia occurred as early as two weeks after initiating etanercept therapy. The causal relationship to etanercept therapy remains unclear. While the majority of patients who developed pancytopenia had recent or concurrent exposure to other anti-rheumatic medications known to be associated with myelosuppression (eg, methotrexate, leflunomide, azathioprine, and cyclophosphamide), some patients had no recent or concurrent exposure to such therapies. Although no high risk group has been identified, caution should be exercised in patients being treated with BRENZYS who have a previous history of significant hematologic

abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (eg, persistent fever, bruising, bleeding, pallor) while on BRENZYS. Discontinuation of BRENZYS therapy should be considered in patients with confirmed significant hematologic abnormalities.

Patients treated with anakinra plus etanercept (3/139, 2%) developed neutropenia ($ANC < 1 \times 10^9/L$). While neutropenic, one of these patients developed cellulitis that resolved with antibiotic therapy.

Malignancies

Lymphomas

In the controlled portions of clinical trials of all the TNF-blocking agents, including etanercept, more cases of lymphoma have been observed among patients receiving the TNF blocker compared to control patients. In controlled and open-label portions of clinical trials of etanercept, the observed rate of lymphoma was 0.10 cases per 100 patient-years. This is 3-fold higher than expected in the general population. Patients with rheumatoid arthritis, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) for the development of lymphoma. Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma that has a very aggressive disease course and is usually fatal, have been reported in patients treated with TNF-blockers. The majority of reported TNF-blocker cases occurred in adolescent and young adult males with Crohn's disease or ulcerative colitis. Almost all of these patients had received treatment with the immunosuppressants azathioprine and/or 6-mercaptopurine concomitantly with a TNF-blocker at or prior to diagnosis.

Leukemia

Cases of acute and chronic leukemia have been reported in association with post-marketing TNF-blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF-blocker therapy, patients with rheumatoid arthritis may be at higher risk (approximately 2-fold) than the general population for the development of leukemia.

During the controlled portions of trials with etanercept, 2 cases of leukemia were observed among 5445 (0.06 cases per 100 patient-years) etanercept-treated patients versus 0 among 2890 (0%) control patients (duration of controlled treatment ranged from 3 to 48 months).

Among 15,401 patients treated with etanercept in controlled and open portions of clinical trials representing approximately 23,325 patient-years of therapy, the observed rate of leukemia was 0.03 cases per 100 patient-years (see ADVERSE REACTIONS/ Malignancies).

Other Malignancies

For malignancies other than lymphoma and non-melanoma skin cancer, there was no difference in exposure-adjusted rates between etanercept, and control arms in the controlled portions of clinical studies for all indications. Analysis of the malignancy rate in combined controlled and uncontrolled portions of studies has demonstrated that types and rates are similar to what is expected in the general population based on the SEER database and suggest

no increase in rates over time.

Whether treatment with BRENZYS might influence the development and course of malignancies in adults is unknown (see ADVERSE REACTIONS/Clinical Trial Adverse Drug Reactions/Malignancies).

Melanoma and Non-melanoma skin cancer (NMSC)

Melanoma and non-melanoma skin cancer (NMSC) have been reported in patients treated with TNF-antagonists, including etanercept. In controlled and open portions of clinical trials among 15,401 patients treated with etanercept, representing approximately 23,325 patient-years of therapy, the observed rate of melanoma was 0.043 cases per 100 patient-years. In controlled clinical trials of rheumatology (RA, AS, PsA) patients, the observed rate of NMSC was 0.41 cases per 100 patient-years in reference product-treated patients compared to 0.37 cases per 100 patient-years among control patients. In controlled clinical trials of psoriasis patients who administered etanercept, the observed rate of NMSC was 3.54 cases per 100 patient-years in reference product-treated patients compared to 1.28 cases per 100 patient-years among control patients (see ADVERSE REACTIONS/Clinical Trial Adverse Drug Reactions/Malignancies). Post-marketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with etanercept.

Risk factors for melanoma or NMSC include cumulative exposure to ultraviolet light, increasing age, male gender, fair complexion, history of acute sunburn or skin cancer, tobacco use, and immunosuppressive agents. Periodic skin examination should be considered for all patients at increased risk for skin cancers.

Pediatric Patients

BRENZYS is not indicated in children. Available data for etanercept treatment in the pediatric population is summarized below:

Malignancies, some fatal, have been reported among children, adolescents and young adults (≤ 22 years of age) who initiated treatment with TNF-blocking agents (initiation of therapy at ≤ 18 years of age), including etanercept. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous post-marketing reports. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. Of these cases, hepatosplenic T-cell lymphoma was not reported in patients treated with etanercept. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. Approximately half of these malignancies occurred in patients being treated for inflammatory bowel disease; approximately one-third of the cases occurred in patients being treated for JIA. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants.

In clinical trials of 696 patients treated with etanercept, representing 1282 patient-years of therapy, no malignancies, including lymphoma or NMSC, have been reported.

Wegener's Granulomatosis

In a randomized placebo controlled study of 180 patients with Wegener's granulomatosis, the addition of etanercept to standard treatment (including cyclophosphamide, methotrexate, and corticosteroids) was no more efficacious than standard therapy alone. Patients receiving etanercept experienced more non-cutaneous malignancies than patients receiving placebo. The role of etanercept in this finding is uncertain due to imbalances between the two arms of the study including age, disease duration, and use of cyclophosphamide. The use of BRENZYS in patients with Wegener's granulomatosis receiving immunosuppressive agents is not recommended. The use of BRENZYS in any patients receiving concurrent cyclophosphamide therapy is not recommended.

General

Parenteral administration of any biologic product should be attended by appropriate precautions in case an allergic or untoward reaction occurs. Allergic reactions associated with administration of etanercept during clinical trials have been reported in < 2% of patients. If any serious allergic or anaphylactic reaction occurs, administration of BRENZYS should be discontinued immediately and appropriate therapy initiated.

Concurrent BRENZYS and anakinra treatment

Serious infections and neutropenia were seen in clinical studies with concurrent use of anakinra and etanercept with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse events seen with combination of etanercept and anakinra therapy, the combination of BRENZYS and anakinra is not recommended (see DRUG INTERACTIONS).

Concurrent BRENZYS and abatacept treatment

In clinical studies, concurrent administration of abatacept and etanercept resulted in increased incidences of serious adverse events and did not demonstrate increased clinical benefit. Use of BRENZYS with abatacept is not recommended (see DRUG INTERACTIONS).

Switching between Biological DMARDS

When switching from one biologic to another, patients should continue to be monitored for signs of infection.

Surgery

There is limited safety experience of surgical procedures in patients treated with etanercept. The half-life of BRENZYS should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on BRENZYS should be closely monitored for infections, and appropriate actions should be taken.

Cardiovascular

Two large clinical trials (2048 patients) evaluating the use of etanercept in the treatment of heart failure were terminated early due to lack of efficacy. There was a suggestion of worse heart failure outcomes in patients with moderate to severe CHF (NYHA ClassIII/IV)

receiving etanercept treatment compared to patients receiving placebo in one of the two trials.

There have been post-marketing reports of worsening of congestive heart failure (CHF), with and without identifiable precipitating factors, in patients taking etanercept. Physicians should exercise caution when using BRENZYS in patients who also have CHF, particularly NYHA Class III/IV.

Immune

Immunosuppression and Immunocompetence

The possibility exists for anti-TNF therapies, including BRENZYS, to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 49 patients with RA treated with etanercept, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cell populations. The role of etanercept in the development and course of malignancies as well as active and/or chronic infections is not fully understood. The safety and efficacy of etanercept in patients with immunosuppression or chronic infections have not been evaluated.

Immunizations

Live vaccines (including yellow fever, BCG, rubella, polio, cholera, typhoid and varicella) should not be given concurrently with BRENZYS. No data are available on the secondary transmission of infection by live vaccines in patients receiving etanercept.

No data are available on the effects of vaccination in RA patients receiving etanercept. Most psoriatic arthritis patients receiving etanercept were able to mount effective B-cell immune response to pneumococcal polysaccharide vaccine, but titers in aggregate were moderately lower and fewer patients had two-fold rises in titers compared to patients not receiving etanercept. The clinical significance of this is unknown. In a study of 205 adult patients with psoriatic arthritis, antibody response to polysaccharide pneumococcal vaccine was similar in patients receiving placebo or etanercept for the following antigens: 9V, 14, 18C, 19F and 23F.

Autoimmunity

Treatment with etanercept may result in the formation of autoantibodies and, rarely, can result in the development of lupus-like syndrome or autoimmune hepatitis, which may resolve following withdrawal of BRENZYS. If a patient develops symptoms and findings suggestive of a lupus-like syndrome or autoimmune hepatitis following treatment with BRENZYS, treatment should be discontinued and the patient should be carefully evaluated.

Hepatic

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 very rare cases with etanercept, has been reported. In the majority of cases, patients were also being treated with

other immunosuppressive drugs, including methotrexate, azathioprine, and/or corticosteroids. Hepatitis B reactivation is not unique to TNF antagonists and has been reported with other immunosuppressive drugs. Therefore, a direct causal relationship to TNF antagonists has not been established. Patients should be evaluated for prior evidence of HBV infection before initiating TNF antagonist therapy. Those previously infected with HBV should be monitored for signs and symptoms of active HBV infection throughout the course of therapy and for several months following discontinuation of therapy.

Use in Patients with Moderate to Severe Alcoholic Hepatitis

Physicians should use caution when using BRENZYS in patients with moderate to severe alcoholic hepatitis. In a study of 48 hospitalized patients treated with etanercept or placebo for moderate to severe alcoholic hepatitis, the mortality rate in patients treated with etanercept was similar to patients treated with placebo at one month but significantly higher after six months. Therefore, the use of BRENZYS for the treatment of patients with alcoholic hepatitis is not recommended.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of etanercept or its effect on fertility. Mutagenesis studies were conducted *in vitro* and *in vivo*, and no evidence of mutagenic activity was observed.

Special Populations

Pregnant Women:

There have been no studies in pregnant women. BRENZYS should not be used during pregnancy unless benefits outweigh the risks (see ADVERSE REACTIONS and WARNINGS AND PRECAUTIONS). BRENZYS has no established use in labour or delivery.

Developmental toxicity studies have been performed with etanercept in rats and rabbits at doses ranging from 60- to 100-fold higher than the human dose and have revealed no evidence of harm to the fetus due to etanercept. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Etanercept crosses the placenta and has been detected in the serum of infants born to women treated with etanercept during pregnancy. The clinical impact of this exposure 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 BRENZYS is generally not recommended.

Nursing Women:

Etanercept has been reported to be excreted in human milk following subcutaneous administration. Because many drugs and immunoglobulins can be excreted in human milk, and because of the potential of serious adverse reactions in nursing infants from BRENZYS, a decision should be made whether to discontinue nursing or to discontinue the drug.

Pediatrics:

BRENZYS is not indicated in children.

Geriatrics (> 65 years of age):

Four hundred and eighty clinical study patients in RA etanercept clinical studies were age 65 or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

One hundred and thirty-eight plaque psoriasis patients in clinical studies performed with etanercept were age 65 or older. In controlled trials of plaque psoriasis, rates of serious adverse events were seen at a frequency of < 1.5% among reference product- and placebo-treated patients in the first 3 months of treatment. However, in patients greater than 65 years of age treated with etanercept 50 mg twice weekly, serious adverse events occurred at a higher rate than in younger patients. In long-term open-label trials of plaque psoriasis serious non-infectious adverse events were infrequent and exposure-adjusted event rates generally remained stable throughout etanercept treatment. Although data for patients aged 65 or greater in the long-term trials are limited, adverse events, including serious adverse events, occurred at a higher frequency for patients treated with 50 mg twice weekly (see ADVERSE REACTIONS/Adverse Drug Reaction Overview).

Greater sensitivity of some older individuals cannot be ruled out. Predisposition of older individuals to infection justifies greater caution when treating the elderly.

Use in Diabetics:

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

ADVERSE REACTIONS

The adverse drug reaction profiles reported in the clinical trials that compared BRENZYS to Enbrel[®] did not show meaningful clinical differences. No new adverse reactions were reported. The description of adverse reactions in this section is based on clinical experience with the reference product Enbrel[®].

Adverse Drug Reaction Overview**Adverse Reactions in Adult Patients with RA or Ankylosing Spondylitis**

Etanercept has been studied in 1442 patients with RA who have been followed for over 6 years, including 225 patients who have been followed for more than 10 years. Etanercept has been studied in 222 patients with ankylosing spondylitis for up to 48 months. Etanercept has over three million patient-years of post-market exposure.

Among patients with RA in placebo-controlled studies, serious adverse events occurred at a frequency of 4% in 349 patients treated with etanercept compared to 5% of 152 placebo-treated patients. In a subsequent study (Study III), serious adverse events occurred at a frequency of 6% in 415 patients treated with etanercept compared to 8% of 217 methotrexate-treated patients. In long-term open-label studies in adults with RA, there were no new or unexpected serious adverse events reported.

In studies with RA patients in placebo-controlled, active-controlled, and open-label trials of etanercept, infections and malignancies were the most common serious adverse events observed. Other infrequent serious adverse events observed in clinical trials with etanercept are listed below by body system:

Cardiovascular:	cardiomyopathy, fainting, heart failure, hypertension, hypotension, myocardial infarction, myocardial ischemia, deep vein thrombosis, thrombophlebitis
Digestive:	cholecystitis, diarrhea, esophageal ulcer, gastrointestinal hemorrhage, pancreatitis, appendicitis
General:	impaired healing, asthenia
Hematologic/Lymphatic:	lymphadenopathy, myelodysplastic syndrome, necrotizing granulomatous lymphadenitis
Hepatic:	hepatic disorder, hepatic steatosis
Musculoskeletal:	bursitis, fistula, fracture nonunion, polymyositis
Nervous:	anxiety, cerebral ischemia, convulsion, depression, multiple sclerosis
Respiratory:	asthma, dyspnea, pulmonary embolism, sarcoidosis
Skin:	worsening psoriasis
Urogenital:	membranous glomerulonephropathy, kidney calculus

In a randomized controlled trial in which 51 patients with RA received etanercept 50 mg twice weekly and 25 patients received etanercept 25 mg twice weekly, the following serious adverse events were observed in the 50 mg twice weekly arm: gastrointestinal bleeding, normal pressure hydrocephalus, seizure, and stroke. No serious adverse events were observed in the 25 mg arm.

In controlled trials, the proportion of patients who discontinued treatment due to adverse events was approximately 4% in both etanercept and placebo treatment groups. The vast majority of these patients were treated with the recommended dose of 25 mg SC twice weekly.

Among patients with rheumatoid arthritis in placebo-controlled studies, deaths occurred in 10 of 2696 (0.37%) etanercept-treated patients compared to 3 of 1167 (0.26%) placebo-treated patients. In controlled and uncontrolled RA studies there were 58 deaths in 6973 patient treated with at least one dose of etanercept over an exposure period of 11,765 patient-years (exposure-adjusted rate of 0.49). In the long-term open-label RA studies, the rate of death did not increase over time with increasing exposure to etanercept.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction

information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse reactions reported in at least 1% of all patients who received etanercept in placebo-controlled RA trials (including the combination methotrexate trial) are outlined in Table 1 below. Adverse reactions reported during ankylosing spondylitis trials were similar to those reported in RA clinical trials.

Table 1. Percent of RA Patients Reporting Adverse Reactions \geq 1% by Body System and Preferred Term in Controlled Trial^a

BODY SYSTEM Preferred Term	Placebo-Controlled Percent of patients		Active-Controlled Percent of patients	
	Placebo (N=152)	Etanercept (N=349)	Methotrexate (N=217)	Etanercept (N=415)
Injection Site Reaction	10	37	7	33
Infection ^b	32	35	72	64
Non-upper respiratory infection ^c	31	39	60	51
Upper respiratory infection ^c	16	29	39	31
Other Adverse Events				
Body as a Whole				
Headache	3	3	13	12
Asthenia	0	1	7	5
Abdominal pain	1	1	5	4
Injection site hemorrhage	0	0	2	4
Pain	1	0	1	1
Mucous membrane disorder	0	1	2	0
Chills	0	0	2	0
Face edema	0	0	1	0
Fever	0	0	1	0
Cardiovascular System				
Vasodilation	1	1	1	1
Hypertension	0	0	0	1
Digestive System				
Nausea	3	2	18	9
Diarrhea	1	1	5	7
Dyspepsia	0	0	3	6
Mouth ulcer	0	1	11	4
Constipation	1	0	3	2
Vomiting	0	0	4	1
Anorexia	0	0	2	1
Flatulence	0	0	2	1
Stomatitis aphthous	0	0	2	1
Dry mouth	0	1	0	1
Stomatitis	0	0	3	0
Hemic & Lymphatic System				
Ecchymosis	1	0	2	2
Metabolic & Nutritional Disorders				
Peripheral edema	0	0	1	2

Weight increased	0	0	1	1
Abnormal healing	0	0	1	0
Musculoskeletal System				
Leg cramps	0	1	1	0
Nervous System				
Dizziness	1	3	5	5
Vertigo	0	0	0	1
Respiratory System				
Rhinitis	2	2	5	4
Dyspnea	0	0	1	3
Pharyngitis	0	1	2	2
Cough increased	1	1	2	1
Epistaxis	0	0	3	0
Voice alteration	0	0	1	0
Skin & Appendages				
Rash	2	3	10	6
Alopecia	0	1	11	5
Pruritus	1	2	1	2
Urticaria	1	0	2	1
Sweat	0	0	1	1
Nail disorder	0	0	2	0
Special Senses				
Dry eye	0	0	0	1
Tinnitus	0	0	0	1
Amblyopia	0	0	1	0

^a Includes data from the double-blinded studies in which patients received concurrent MTX therapy.

^b Infection (total) includes data from all three placebo-controlled trials. Body system and relationship to study drug was not collected for infections.

^c Non-URI and URI include data only from two placebo-controlled trials where infections were collected separately from adverse events (placebo N = 110, Reference product N = 213).

N = Number of patients having received at least 1 dose of study drug

% = n/N*100

Less Common Clinical Trial Adverse Drug Reactions (< 1%)

The following adverse reactions were reported at an incidence of < 1% (occurring in more than 1 patient, with higher frequency than placebo): **Body as a Whole:** enlarged abdomen, general edema, hernia, infection, injection site reaction, malaise, overdose, Sjogrens syndrome; **Cardiovascular:** cerebrovascular accident, hypotension, myocardial infarction, phlebitis, deep thrombophlebitis; **Gastrointestinal:** increased appetite, colitis, dysphagia, glossitis, gum hemorrhage, rectal hemorrhage; **Hemic and Lymphatic System:** petechia; **Metabolic and Nutritional Disorders:** edema, hypercholesteremia, hyperglycemia; **Musculoskeletal System:** arthrosis, bone disorder, fibrosis tendon, bone necrosis; **Nervous System:** nervousness, neuropathy; **Respiratory System:** bronchitis, lung carcinoma, hemoptysis, laryngitis; **Skin and Appendages:** skin carcinoma, dermatitis exfoliative, skin hypertrophy, skin discoloration, skin ulcer; **Special Senses:** corneal lesion, ear disorder, eye hemorrhage, otitis media; **Urogenital System:** cervix disorder, cystitis, dysuria, gynecomastia, uterine hemorrhage, kidney polycystic, cervix neoplasm, polyuria, urine urgency.

Injection Site Reactions

In controlled trials with etanercept in rheumatologic indications, approximately 37% of patients treated with etanercept developed injection site reactions. In post- marketing experience, there have been reported cases (1.8% of all patients treated) of injection site bleeding and bruising observed in conjunction with etanercept therapy.

Infections

The percent of patients reporting infections in controlled studies of etanercept in rheumatoid arthritis and ankylosing spondylitis is provided in Table 2. The most common type of infection was upper respiratory infection.

Table 2. Percent of Patients Reporting Infections Across Controlled Studies in Rheumatoid Arthritis and Ankylosing Spondylitis

	Event		
	Total Infection	Non-URI	URI
Rheumatoid Arthritis (Placebo-Controlled)			
Placebo (N=152)	32%	31%	16%
Etanercept (N=349)	35%	39%	29%*
Rheumatoid Arthritis (Active-Controlled)			
MTX (N=217)	72%	60%	39%
Etanercept (N=415)	64%*	51%	31%
Ankylosing Spondylitis			
Placebo (N=139)	30%	20%	12%
Etanercept (N=138)	41%	24%	20%*

URI = Upper Respiratory Infection

*Fisher's exact p-value < 0.05

For dose and regimen of the reference product in each indication, please refer to Part II Clinical Trials section.

In placebo-controlled trials conducted with etanercept in RA, and ankylosing spondylitis no increase in the incidence of serious infections was observed (approximately 1% in both placebo- and etanercept-treated groups). In all clinical trials in RA, serious infections experienced by patients have included pyelonephritis, bronchitis, septic arthritis, abdominal abscess, cellulitis, osteomyelitis, wound infection, pneumonia, foot abscess, leg ulcer, diarrhea, sinusitis and sepsis. The rate of serious infections has not increased in open-label extension trials and is similar to that observed in controlled trials (Table 3). Serious infections, including sepsis and death, have also been reported during post-marketing use of etanercept. Some have occurred within a few weeks after initiating treatment with etanercept. Many of the patients had underlying conditions (eg, diabetes, congestive heart failure, history of active or chronic infections) in addition to their RA. Data from a sepsis clinical trial not specifically in patients with RA suggest that etanercept treatment may increase mortality in patients with established sepsis.

Table 3. Serious Infections over Time

All etanercept* (N = 1341)			
Year	Number of patients	Number of patients with events	Incidence rate
1	1341	35	0.026
2	1113	26	0.023
3	1006	26	0.026
4	915	25	0.027
5	849	27	0.032
6	769	22	0.029
7	696	21	0.030
8	647	24	0.037
9	608	16	0.026
10	529	15	0.028

*Controlled trials and open-label extension studies in RA.

In a controlled trial in patients with ankylosing spondylitis, rates of infection were also similar to those observed in the controlled studies of patients with RA or psoriatic arthritis. No increase in the incidence of serious infections was observed in patients treated with etanercept.

In 2 studies in which patients were receiving both etanercept and anakinra for up to 24 weeks, the incidence of serious infections was 7%. The most common infections consisted of bacterial pneumonia (4 cases) and cellulitis (4 cases). One patient with pulmonary fibrosis and pneumonia died due to respiratory failure.

In global etanercept clinical studies of 20,070 patients (28,308 patient-years of therapy), tuberculosis was observed in approximately 0.01% of patients. In 15,438 patients (23,524 patient-years of therapy) from clinical studies in the US and Canada, tuberculosis was observed in approximately 0.007% of patients. These studies include reports of pulmonary and extra-pulmonary tuberculosis (see WARNINGS and PRECAUTIONS/Serious and Opportunistic Infections section).

In 38 etanercept clinical trials and 4 cohort studies in all approved indications representing 27,169 patient-years of exposure (17,696 patients) from the United States and Canada, no histoplasmosis infections were reported among patients treated with etanercept. Data from clinical studies and post-marketing reports suggest that differences may exist in the risk of invasive histoplasmosis infection among TNF blockers. Nonetheless, post-marketing cases of serious and sometimes fatal fungal infections, including histoplasmosis, have been reported with TNF blockers, including etanercept (see WARNINGS and PRECAUTIONS/Serious and Opportunistic Infections section).

In post-marketing experience infections have been observed with various pathogens including viral, bacterial, mycobacterial, invasive fungal, and parasitic (including protozoal) organisms. Infections, including opportunistic infections (including atypical mycobacterial infection, herpes zoster, aspergillosis, *Pneumocystis jiroveci* pneumonia, histoplasmosis, candidiasis, coccidioidomycosis, listeriosis and legionellosis), have been reported in patients receiving etanercept alone or in combination with immunosuppressive agents.

Malignancies

Information is available from 10,953 adult patients with 17,123 patient-years and 696 pediatric patients with 1282 patient-years of experience across 45 etanercept clinical studies.

In an open-label extension study that followed 581 DMARD-refractory RA patients for more than 10 years, the standardized incidence ratio (SIR) for all malignancies with respect to corresponding SEER rate was 1.30 with the 95% confidence interval (CI) of 0.97 to 1.71. In an open-label extension study that followed 468 early active RA patients for up to 9.6 years, the SIR for all malignancies with respect to corresponding SEER rate was 1.39 with the 95% CI of 0.98 to 1.93.

Lymphomas

An increased rate of lymphoma up to several-fold has been reported in the RA patient population, and may be further increased in patients with more severe disease activity.

In the controlled portions of clinical trials of TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared to control patients. During the controlled portions of etanercept trials in adult patients with RA, AS, and PsA, 2 lymphomas were observed among 3306 etanercept-treated patients versus 0 among 1521 control patients (duration of controlled treatment ranged from 3 to 36 months).

Among 6543 adult rheumatology (RA, PsA, AS) patients treated with etanercept in controlled and uncontrolled portions of clinical trials, representing approximately 12,845 patient-years of therapy, the observed rate of lymphoma was 0.10 cases per 100 patient-years. This was 3-fold higher than the rate of lymphoma expected in the general population based on the SEER database.

In an open-label extension study that followed 581 DMARD-refractory RA patients for more than 10 years, the SIR for lymphomas with respect to corresponding SEER rate was 4.49 with a 95% CI of 1.81 to 9.26. In an open-label extension study that followed 468 early active RA patients for up to 9.6 years, the SIR for lymphomas with respect to corresponding SEER rate was 7.76 with a 95% CI of 3.35 to 15.30.

Leukemia

Cases of acute and chronic leukemia have been reported in association with post-marketing TNF-blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF-blocker therapy, patients with rheumatoid arthritis may be at higher risk (approximately 2-fold) than the general population for the development of leukemia.

During the controlled portions of etanercept trials, 2 cases of leukemia were observed among 5445 (0.06 cases per 100 patient-years etanercept-treated patients versus 0 among 2890 (0%) control patients (duration of controlled treatment ranged from 3 to 48 months).

Among 15,401 patients treated with etanercept in controlled and open portions of clinical trials representing approximately 23,325 patient-years of therapy, the observed rate of leukemia was 0.03 cases per 100 patient-years.

Other Malignancies

For malignancies other than lymphoma and non-melanoma skin cancer, there was no difference in exposure-adjusted rates between etanercept and control arms in the controlled portions of clinical studies for all indications. Analysis of the malignancy rate in combined controlled and uncontrolled portions of studies has demonstrated that types and rates are similar to what is expected in the general population based on the SEER database and suggest no increase in rates over time.

Whether treatment with etanercept might influence the development and course of malignancies in adults is unknown.

Melanoma and Non-melanoma skin cancer (NMSC)

Melanoma and non-melanoma skin cancer (NMSC) have been reported in patients treated with TNF-antagonists, including etanercept. Among 15,401 patients treated with etanercept in controlled and open portions of clinical trials representing approximately 23,325 patient-years of therapy, the observed rate of melanoma was 0.043 cases per 100 patient-years. Among 3306 adult rheumatology patients treated with etanercept in controlled clinical trials, representing approximately 2669 patient-years of therapy, the observed rate of NMSC was 0.41 cases per 100 patient-years vs. 0.37 cases per 100 patient-years among 1521 control patients representing 1077 patient-years.

Among 89 patients with Wegener's granulomatosis receiving etanercept in a randomized, placebo-controlled trial, 5 experienced a variety of non-cutaneous solid malignancies compared with none receiving placebo (see WARNINGS AND PRECAUTIONS/ Wegener's granulomatosis).

Autoantibodies

Patients had serum samples tested for autoantibodies at multiple time points. In RA Studies I and II, the percentage of patients evaluated for antinuclear antibodies (ANA) 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. In Study III, no pattern of increased autoantibody development was seen in etanercept patients compared to methotrexate patients.

The impact of long-term treatment with etanercept on the development of autoimmune diseases is unknown. Rare adverse event reports have described patients with rheumatoid factor positive and/or erosive RA who have developed additional autoantibodies in conjunction with rash and other features suggesting a lupus-like syndrome.

Immunogenicity

Patients with RA, or psoriatic arthritis, ankylosing spondylitis or plaque psoriasis were tested

at multiple time points for antibodies to etanercept. Non-neutralizing antibodies to the TNF receptor portion or other protein components of the reference drug product were detected at least once in sera of approximately 6% of adult patients with RA, psoriatic arthritis, ankylosing spondylitis or plaque psoriasis. In long-term plaque psoriasis studies up to 144 weeks, the percentage of patients testing positive at any time point assessed was 3%-10%. Results from JIA patients were similar to those seen in adult RA patients treated with etanercept. In all clinical studies with etanercept to date, there has been no apparent correlation of antibody development to clinical response or adverse events. Neutralizing antibodies have not been observed with etanercept.

The data reflect the percentage of patients whose test results were considered positive for antibodies to etanercept in an ELISA assay and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of any antibody positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to etanercept with incidence of antibodies to other products may be misleading.

Patients with Heart Failure

Two randomized placebo-controlled studies have been performed in patients with CHF. In one study, patients received either etanercept 25 mg twice weekly, 25 mg three times weekly, or placebo. In a second study, patients received either etanercept 25 mg once weekly, 25 mg twice weekly, or placebo. Results of the first study suggested higher mortality in patients treated with etanercept at either schedule compared to placebo. Results of the second study did not corroborate these observations. Analyses did not identify specific factors associated with increased risk of adverse outcomes in heart failure patients treated with etanercept (see WARNINGS AND PRECAUTIONS/ Cardiovascular).

Adverse Reactions in Pediatric Patients

The safety of BRENZYS has not been established in pediatric patients.

Other

In a study with etanercept manufactured by a modified process (see PART II/ CLINICAL TRIALS/ Other Studies) major adverse events included the following. Twelve patients (5.4%) experienced 13 serious adverse events. One patient experienced a benign lung neoplasm. One patient (0.4%) experienced a life-threatening non-infectious event (pulmonary embolism) and 14 patients (6.3%) experienced severe non-infectious adverse events. One serious event (urinary tract infection) was considered infectious. One adverse event of hepatic neoplasm malignant (serious) and one squamous cell carcinoma (non-serious) were reported. Overall, the safety profile was comparable to the etanercept manufactured using the previous process.

Post-Market Adverse Drug Reactions

Additional adverse events have been identified during post-marketing use of etanercept. Because these events 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 etanercept exposure. These adverse events include, but are not limited to, the following

(listed by body system):

Body as a Whole:	angioedema, fatigue, fever, flu syndrome, generalized pain, weight gain
Cardiovascular:	chest pain, vasodilation (flushing), new-onset congestive heart failure
Digestive:	altered sense of taste, anorexia, diarrhea, dry mouth, intestinal perforation
Hematologic/Lymphatic:	adenopathy, anemia, aplastic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia
Hepatobiliary:	autoimmune hepatitis, elevated transaminase, hepatitis B reactivation
Immune:	macrophage activation syndrome, systemic vasculitis
Musculoskeletal:	joint pain, lupus-like syndrome with manifestations including rash consistent with subacute or discoid lupus
Neoplasms benign, malignant and unspecified	Merkel cell carcinoma
Nervous:	paresthesias, stroke, seizures and central nervous system events suggestive of multiple sclerosis or isolated demyelinating conditions such as transverse myelitis or optic neuritis
Ocular:	dry eyes, ocular inflammation, scleritis, uveitis
Respiratory:	dyspnea, interstitial lung disease, pulmonary disease, worsening of prior lung disorder
Skin:	cutaneous vasculitis, including leukocytoclastic vasculitis (with several symptom manifestations), erythema multiforme, Stevens- Johnson syndrome, toxic epidermal necrolysis, pruritus, subcutaneous nodules, urticaria, new or worsening psoriasis (all sub-types including pustular and palmoplantar)

DRUG INTERACTIONS

Overview

Specific drug interaction studies have not been conducted. Etanercept has not been formally evaluated in combination with other DMARDs such as gold, antimalarials, sulfasalazine, penicillamine, azathioprine, cyclophosphamide, or leflunomide and the benefits and risks of such combinations are unknown.

Drug-Drug Interactions

Etanercept can be used in combination with methotrexate in adult patients with rheumatoid arthritis.

No clinically significant pharmacokinetic drug-drug interactions were observed in studies with digoxin and warfarin.

Patients in a clinical study who were on established therapy with sulfasalazine, to which

etanercept was added, experienced a statistically significant decrease in mean white blood cell counts in comparison to groups treated with either etanercept or sulfasalazine alone. The significance of this observation is unknown.

Concurrent introduction of etanercept and anakinra therapies has not been associated with increased clinical benefit to patients. In a study in which patients with active RA were treated for up to 24 weeks with concurrent etanercept and anakinra therapy, a 7% rate of serious infections was observed, which was higher than that observed with etanercept alone (0%). Two percent of patients treated concurrently with etanercept and anakinra developed neutropenia ($ANC < 1 \times 10^9/L$).

In a study of patients with Wegener's granulomatosis, the addition of etanercept to standard therapy (including cyclophosphamide) was associated with a higher incidence of non-cutaneous malignancies. Although the role of etanercept in this finding is uncertain, the use of BRENZYS in any patients receiving concurrent cyclophosphamide therapy is not recommended.

In clinical studies, concurrent administration of abatacept and etanercept resulted in increased incidences of serious adverse events and did not demonstrate increased clinical benefit. Use of BRENZYS with abatacept is not recommended.

DOSAGE AND ADMINISTRATION

Dosing Considerations

BRENZYS is intended for use under the guidance and supervision of a physician who has sufficient knowledge of RA, or ankylosing spondylitis and who has fully familiarized himself/herself with the efficacy/safety profile of BRENZYS. Patients may self-inject only if their physician determines that it is appropriate and with medical follow-up, as necessary, after proper training in measurement of the correct dose and injection technique.

Recommended Dose and Dosage Adjustment

A 50 mg dose should be given as one subcutaneous (SC) injection.

Adult RA and Ankylosing Spondylitis Patients

The recommended dose of BRENZYS for adult patients with rheumatoid arthritis, or ankylosing spondylitis is 50 mg per week. Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics may be continued during treatment with BRENZYS. Based on a study of 50 mg etanercept twice weekly in patients with RA that suggested higher incidence of adverse reactions but similar American College of Rheumatology (ACR) response rates, doses higher than 50 mg per week are not recommended.

Missed Dose

Patients who miss a dose of BRENZYS should be advised to contact their doctor to find out when to take their next dose of BRENZYS.

Administration

Preparation of BRENZYS Using the Single-use Pre-filled Syringe or Single-use Pre-filled Auto-injector:

Before injection, allow BRENZYS to reach room temperature (approximately 30 minutes). DO NOT remove the needle cap while allowing the pre-filled syringe or pre-filled auto-injector to reach room temperature.

Prior to administration, visually inspect the solution for particulate matter and discoloration. There may be small white particles of protein in the solution. This is not unusual for proteinaceous solutions. The solution should not be used if discoloured or cloudy, or if foreign particulate matter is present.

OVERDOSAGE

The maximum tolerated dose of etanercept has not been established in humans. Toxicology studies have been performed with etanercept in monkeys at doses up to 30 times the human dose with no evidence of dose-limiting toxicities. No dose-limiting toxicities have been observed during clinical trials of etanercept. Single IV doses up to 60 mg/m² have been administered to 32 healthy volunteers (25 males, 7 females) in an endotoxemia study without evidence of dose-limiting toxicities. The highest dose level evaluated in RA patients has been a single IV loading dose of 32 mg/m² followed by SC doses of 16 mg/m² (~ 25 mg) administered twice weekly. In one RA trial, one patient mistakenly self-administered 62 mg etanercept SC twice weekly for 3 weeks without experiencing adverse effects.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Etanercept is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) tumour necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1. It consists of 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons.

Etanercept binds specifically to soluble and cell surface tumour necrosis factor (TNF) and blocks its interaction with cell surface TNF receptors. Etanercept inactivates TNF without causing *in vitro* lysis of cells involved in the immune response. TNF is a naturally occurring cytokine, or immune system protein, that is implicated in the development and progression of inflammatory, infectious, and autoimmune diseases. TNF plays an important role in the inflammatory processes of rheumatoid arthritis (RA), ankylosing spondylitis and the resulting joint pathology. Elevated levels of TNF are found in the synovial fluid of RA patients, and in serum and synovial tissue of patients with ankylosing spondylitis.

Two distinct receptors for TNF (TNFRs), a 55 kilodalton protein (p55) and a 75 kilodalton

protein (p75), exist naturally as monomeric molecules on cell surfaces and in soluble forms. Biological activity of TNF is dependent upon binding to either cell surface TNFR.

Etanercept is a dimeric soluble form of the p75 TNF receptor that can bind to two TNF molecules. This dimeric binding provides substantially greater competitive inhibition of TNF than monomeric soluble receptors.

Much of the joint pathology in RA is mediated by proinflammatory molecules that are linked in a network controlled by TNF.

Etanercept competitively inhibits binding of both TNF α and TNF β (lymphotoxin α [LT α]) to cell surface TNF receptors, rendering TNF biologically inactive. Etanercept does not cause lysis of TNF-producing cells *in vitro*, in the presence or absence of complement.

Pharmacodynamics

Etanercept also modulates biological responses that are induced or regulated by TNF, including expression of adhesion molecules responsible for leukocyte migration (i.e., E-selectin and to a lesser extent intercellular adhesion molecule-1 [ICAM-1]), serum levels of cytokines (eg, IL-6, IL-1), and serum levels of matrix metalloproteinase-3 (MMP-3 or stromelysin). Etanercept has been shown to affect several animal models of inflammation, including murine collagen-induced arthritis.

Pharmacokinetics

After administration of 25 mg etanercept by a single subcutaneous (SC) injection to 25 patients with RA, a mean \pm standard deviation half-life of 102 ± 30 hours was observed with a clearance of 160 ± 80 mL/hr. A maximum serum concentration (C_{\max}) of 1.1 ± 0.6 mcg/mL and time to C_{\max} of 69 ± 34 hours was observed in these patients following a single 25 mg dose. After 6 months of twice weekly 25 mg doses in these same RA patients, the mean C_{\max} was 2.4 ± 1.0 mcg/mL ($N = 23$). Patients exhibited a two- to seven-fold increase in peak serum concentrations and approximately four-fold increase in $AUC_{0-72 \text{ hr}}$ (range 1 to 17 fold) with repeated dosing. Serum concentrations in patients with RA have not been measured for periods of dosing that exceed 6 months. In another study, serum concentration profiles at steady state were comparable among patients with RA treated with 50 mg etanercept once weekly and those treated with 25 mg etanercept twice weekly. The mean (\pm standard deviation) C_{\max} , C_{\min} , and partial AUC were 2.4 ± 1.5 mg/L, 1.2 ± 0.7 mg/L, and 297 ± 166 mg•h/L, respectively, for patients treated with 50 mg etanercept once weekly ($N = 21$); and 2.6 ± 1.2 mg/L, 1.4 ± 0.7 mg/L, and 316 ± 135 mg•h/L for patients treated with 25 mg etanercept twice weekly ($N = 16$).

Special Populations and Conditions

Gender: Pharmacokinetic parameters were not different between men and women and did not vary with age in adult patients.

Hepatic Insufficiency: No formal pharmacokinetic studies have been conducted to examine the effect of hepatic impairment on etanercept disposition or potential interactions with methotrexate.

Renal Insufficiency: No formal pharmacokinetic studies have been conducted to examine the effect of renal impairment on etanercept disposition or potential interactions with methotrexate.

STORAGE AND STABILITY

BRENZYS Single-use Pre-filled Syringe and BRENZYS Single-use Pre-filled Auto-injector: BRENZYS should be stored refrigerated at 2°C to 8°C. **DO NOT FREEZE.** Keep the product in the original carton to protect from light until the time of use. Do not shake. Keep in a safe place out of the reach of children.

Do not use BRENZYS beyond the expiration date stamped on the carton, syringe or auto-injector label. BRENZYS may be transferred to room temperature storage ($\leq 27^{\circ}\text{C}$) for a period not to exceed 60 days. Once transferred to room temperature storage, BRENZYS must be used within 60 days. Protect from direct sunlight, sources of heat, and humidity.

SPECIAL HANDLING INSTRUCTIONS

BRENZYS is provided as a single-use pre-filled syringe and a single-use pre-filled auto-injector.

If a patient or caregiver is to administer BRENZYS, he/she should be instructed in injection techniques and how to measure the correct dose to ensure the safe administration of BRENZYS. The first injection should be performed under the supervision of a qualified health care professional. The patient's or caregiver's ability to inject subcutaneously should be assessed. Alcohol swabs and cotton balls or gauze are required for the injections and will need to be obtained separately. A puncture-resistant container for disposal of syringes and auto-injectors should be used. Patients and caregivers should be instructed in the technique of proper syringe disposal, and be cautioned against reuse of these items.

DOSAGE FORMS, COMPOSITION AND PACKAGING

BRENZYS single-use pre-filled syringes are available as a 50 mg dosage strength (0.98 mL of a 50 mg/mL solution of etanercept, minimum deliverable volume of 0.94 mL).

BRENZYS single-use pre-filled auto-injectors are available as a 50 mg dosage strength (0.98 mL of a 50 mg/mL solution of etanercept, minimum deliverable volume of 0.93 mL). Pre-filled syringes and auto-injectors are intended for subcutaneous injection.

The solution of BRENZYS is clear and colorless, sterile, preservative free, and is formulated at $\text{pH } 6.2 \pm 0.3$. There may be small white particles of protein in the solution. Each BRENZYS single-use pre-filled syringe and pre-filled auto-injector contains 50 mg/mL solution of etanercept with 1% sucrose, 140 mM sodium chloride and 10 mM sodium phosphate.

BRENZYS 50 mg single-use pre-filled syringes and BRENZYS 50 mg single-use pre-filled

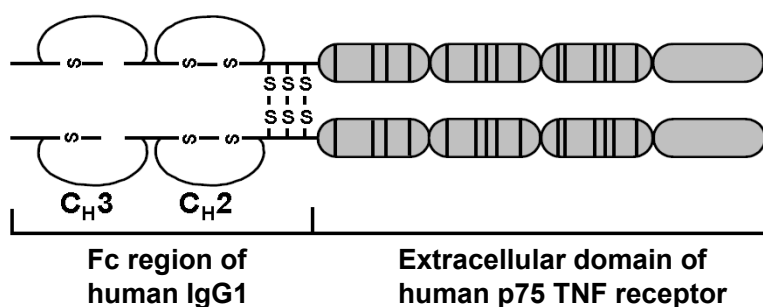
auto-injectors are supplied in cartons containing four syringes or pens with 27-gauge, ½ inch needles.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Etanercept
Chemical name:	Etanercept is not a chemical. Etanercept is a Recombinant human Tumour Necrosis Factor Receptor: Fusion Protein (TNFR:Fc)
Molecular formula and molecular mass:	Etanercept consists of 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons. The relative activity of BRENZYS is 100% compared to Enbrel [®] .
Structural formula:	



Physicochemical properties:	BRENZYS is a clear and colorless, sterile, preservative free solution, and is formulated at pH 6.2 ± 0.3 . There may be small white particles of protein in the solution. This is not unusual for proteinaceous solutions. Each BRENZYS single-use pre-filled syringe and pre-filled auto-injector contains a 50 mg/mL solution of etanercept, with 1% sucrose, 140 mM sodium chloride and 10 mM sodium phosphate.
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Product Characteristics

Etanercept is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human p75 tumour necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1 (see illustration above). Etanercept is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system for use as a therapeutic inhibitor of tumour necrosis factor (TNF), a proinflammatory cytokine. Etanercept is composed entirely of human amino acid sequences. The Fc component of etanercept contains the CH2 and CH3 domains but not the CH1 domain of IgG1.

CLINICAL TRIALS

BRENZYS is a subsequent entry biologic product to Enbrel[®] (etanercept).

The clinical development program to show clinical comparability between BRENZYS and the reference product is based on

- Clinical phase I study SB4-G11-NHV in healthy male subjects.
- Clinical Phase III study SB4-G31-RA in patients with moderate to severe RA despite

MTX therapy.

A brief overview of the trial design and study demographics of the clinical studies is presented in Table 4.

Table 4. Study Demographics and Trial Design

Study Number	Type of Study	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (years; range)	Gender
SB4-G11-NHV	Phase I: Comparative PK, Safety / Tolerability, Immunogenicity Equivalence Study	Randomized, single-blind, three-part, two-period, two-sequence (1:1 ratio), single-dose, cross-over study	Etanercept 50 mg/mL <u>Part A:</u> BRENZYS 50 mg, EU Enbrel® 50 mg, Single dose, SC <u>Part B:</u> BRENZYS 50 mg, US Enbrel® 50 mg, Single dose, SC <u>Part C:</u> EU Enbrel® 50 mg, US Enbrel® 50 mg, Single dose, SC Period 1: 21 days Period 2: 21 days Treatment periods separated by 7 days, resulting in washout of 28 days	Healthy male subjects N=138 Part A: n=46 Part B: n=46 Part C: n=46	40 19-55 Part A: 39 Part B: 40 Part C: 41	Male: n=138 (100%)
SB4-G31-RA	Phase III: Comparative Efficacy, Safety / Tolerability, Immunogenicity Steady-state PK	Randomized, double-blind, two-arm (1:1 ratio), parallel-group, multicentre study	Etanercept 50 mg/mL (for 52 weeks), MTX background treatment <u>BRENZYS arm:</u> BRENZYS 50 mg,	Patients with moderate to severe rheumatoid arthritis (RA) despite MTX therapy	51.8 19-75 BRENZYS: 52.1 Enbrel®: 51.6	BRENZYS Male: n=50 (16.7%) Female: n=249 (83.3%) Enbrel®

Study Number	Type of Study	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (years; range)	Gender
	Equivalence Study		once weekly, SC Enbrel [®] arm: EU Enbrel [®] 50 mg, once weekly, SC 52-week active treatment period (plus 4-week safety follow-up)	N=596 (BRENZYS: 299; Enbrel [®] : 297)		Male: n=44 (14.8%) Female: n=253 (85.2%)

MTX: methotrexate; PK: Pharmacokinetics; RA: rheumatoid arthritis; SC: subcutaneous;

Comparative Pharmacokinetic Studies

Comparative Pharmacokinetic Study SB4-G11-NHV

Study SB4-G11-NHV is a controlled, randomized, single-blind, 3-part, 2-period, 2-sequence, single-dose, cross-over study to compare the PK, safety / tolerability, and immunogenicity of three formulations of etanercept (BRENZYS, EU Enbrel[®], US Enbrel[®]), in healthy male subjects.

The study evaluated 138 healthy male subjects. The study comprised three parts (Part A, B, and C) to demonstrate comparability between BRENZYS and EU Enbrel[®], between BRENZYS and US Enbrel[®] and between EU Enbrel[®] and US Enbrel[®], respectively.

In each period, a single dose of 50 mg was given and then followed for 21 days to assess PK, safety, tolerability and immunogenicity of etanercept.

Study Results

Following a single dose administration of either BRENZYS or EU sourced Enbrel[®], comparability criteria were met for etanercept PK parameters C_{max} and AUC_{last} . Only Part A of the study uses the named reference suitable for the Canadian context (EU Enbrel[®]), and the results will be restricted to this comparison (Brenzys vs. EU Enbrel[®]).

In Part A, the point estimate for the BRENZYS/EU Enbrel[®] mean ratios for C_{max} was 103.71% and the 90% CI for AUC_{last} parameter was 94.17% to 103.28%. Both estimates were within the acceptance interval of 80.00% to 125.00% (See Table 5).

Part A (BRENZYS vs. EU Enbrel[®])

The comparative serum concentration-time profile of BRENZYS and EU Enbrel[®] is depicted in Figure 1.

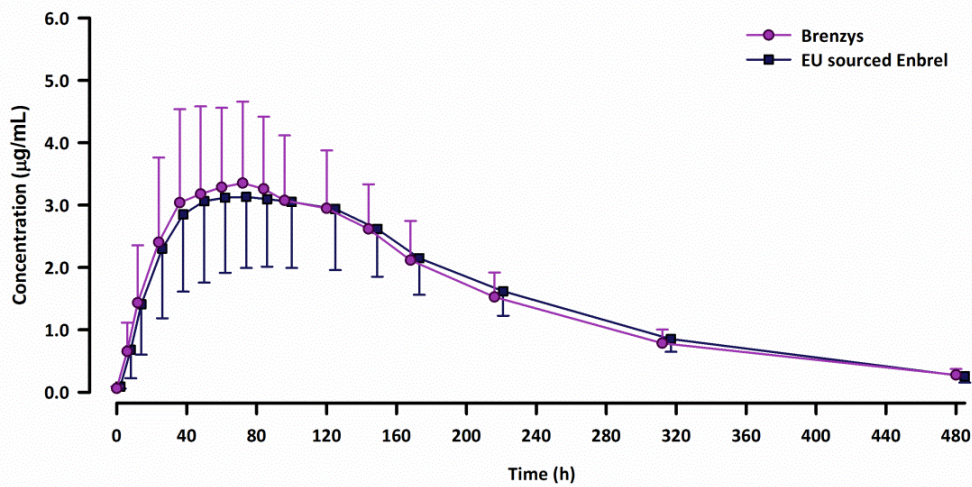


Figure 1. Mean Serum Concentrations versus Nominal Times on Semi-logarithmic Scale in Part A (BRENZYS vs. EU Enbrel[®]) (Study SB4-G11-NHV)

The serum concentrations of BRENZYS and Enbrel[®] were measured at the same timepoint. In order to facilitate the readability of the graph, the Enbrel[®] curve has been slightly shifted to the right for the clear display of SD.

The pharmacokinetic comparability of BRENZYS and EU Enbrel[®] are shown in Table 5.

Table 5. Statistical Comparison of Primary PK Parameters in Part A (BRENZYS vs. EU Enbrel[®]; PK Population) (Study SB4-G11-NHV)

	Treatment	N	n	Geometric LSMeans	Ratio (%)	90% CI (%) (lower; upper)	Intra-CV%
C _{max} (µg/mL)	BRENZYS	45	42	3.319	103.71		14.205
	EU Enbrel [®]	45	42	3.201			
AUC _{last} (µg·h/mL)	BRENZYS	45	42	688.853	98.62	94.17; 103.28	12.603
	EU Enbrel [®]	45	42	698.494			

A: BRENZYS; B: EU Enbrel[®]; AUC_{last}: area under the concentration-time curve from time zero to the last quantifiable concentration; CI: confidence interval; C_{max}: maximum concentration; CV%: coefficient of variation; LSMeans: least squares means; N: number of subjects in PK population; n: number of subjects who contributed to analysis; Three subjects were excluded due to carryover effect.

Table 6. Pharmacokinetic Parameters after a Single Dose of Etanercept in Healthy Subjects in Part A (BRENZYS vs. EU Enbrel®; PK Population) (Study SB4-G11-NHV)

Parameter	Statistics	Part A	
		BRENZYS N = 45	EU Enbrel® N = 45
AUC _{inf} (µg·h/mL)	n	42	42
	Mean	769.069	771.680
	SD	243.9039	226.2874
C _{max} (µg/mL)	n	42	42
	Mean	3.607	3.435
	SD	1.4298	1.2390
AUC _{last} (µg·h/mL)	n	42	42
	Mean	728.169	734.015
	SD	234.7621	220.2722
T _{max} (h)	n	42	42
	Median	72.025	71.992
	Min, Max	35.933, 145.817	35.983, 143.583
t _{1/2} (h)	n	42	42
	Mean	105.782	100.340
	SD	11.6924	16.1335
CL/F (L/h)	n	42	42
	Mean	0.073	0.072
	SD	0.0275	0.0248
V _z /F (L)	n	42	42
	Mean	11.203	10.511
	SD	4.7490	4.7073

Three subjects in Part A were excluded due to carryover effect.

AUC_{last}: area under the concentration-time curve from time zero to the last quantifiable concentration AUC_{inf}: area under the concentration-time curve from time zero to infinity; CL/F: apparent total body clearances; C_{max}: maximum concentration; Max: maximum; Min: minimum; N: number of subjects in PK population; n: number of subjects who contributed to summary statistics; T_{max}: time to C_{max}; t_{1/2}: terminal half-life; V_z/F: apparent volume of distribution during terminal phase.

Comparative Clinical Efficacy and Safety Studies

Adult Rheumatoid Arthritis

Study SB4-G31-RA evaluated efficacy, safety / tolerability, pharmacokinetic and immunogenicity of BRENZYS and the reference product.

This study evaluated 596 patients who were 18-75 years old with moderate to severe active disease despite MTX therapy (6 months ≤ disease duration < 15 years); and had more than or equal to six swollen joints and more than or equal to six tender joints (from the 66/68 joint

count system), and either erythrocyte sedimentation rate (ESR) \geq 28 mm/h or serum C-reactive protein (CRP) \geq 1.0 mg/dL. Doses of 50 mg of either BRENZYS or Enbrel[®] were administered once-weekly up to 52 weeks via subcutaneous injection. In addition to etanercept, each patient also took a stable dose of oral or parenteral MTX (10-25 mg weekly) and was required to take folic acid 5-10 mg weekly while taking MTX.

The study evaluated the ACR20 response based on at least 20% improvement from baseline in swollen joint count (66 joint count); at least a 20% improvement from baseline in tender joint count (68 joint count) and at least a 20% improvement from baseline in at least three of the following: Subject pain assessment a 100mm visual analogue scale (VAS); subject global assessment using a 100 mm VAS; Physician Global assessment using a 100mm VAS; subjects assessment of disability using Health Assessment –Disability Index (HAQ-DI); and/or acute phase reactant level (CRP). Also evaluated were disease activity score based on 28 joint count (DAS28) and sharp radiographic score.

Study Results

The ACR20 response rates at Week 24 were comparable between BRENZYS and Enbrel[®] in the per-protocol set 1 (PPS1). The proportions of patients achieving ACR20 response in the PPS1 were 78.1% (193/247) and 80.5% (190/236) in the BRENZYS and Enbrel[®] treatment groups, respectively. The adjusted treatment difference was -2.37% and the 95% CI of the adjusted treatment difference [-9.54% , 4.80%] was completely within the pre-defined equivalence margin of [-15% , 15%] (Table 7).

In the FAS, the ACR20 response rates were 73.6% (220/299) and 71.7% (213/297) in the BRENZYS and Enbrel[®] treatment groups, respectively. The adjusted treatment difference in ACR20 response rate at Week 24 with non-responder analysis in FAS was 1.66% and the 95% CI was [-5.50% , 8.82%] which was completely within the pre-defined equivalence margin of [-15% , 15%] (Table 8).

The time-response curves of BRENZYS and Enbrel[®] up to Week 24 showing the ACR20 response over time were estimated to be equivalent and supported the robustness of the primary efficacy analysis for the PPS1. The 2-norm of the treatment difference was 10.8 and the 95% CI of the treatment difference was [-6.2 , 27.9], where the upper limit 27.9 was less than the pre-specified equivalence margin of 83.28. The 2-norm was measured as the sum of squared treatment difference up to Week 24. The time-response curves for the ACR20 responses up to Week 24 for the PPS1 are presented in Figure 2.

To determine the comparability, the equivalence limit of the change in DAS28 was chosen as 0.6, which is half of the minimum score of clinically significant improvement (1.2) in DAS28 based on EULAR response criteria. The treatment difference in the LSM means of the change in DAS28 score at Week 24 and Week 52 was 0.072 (95% CI [-0.135 , 0.279]) and 0.118 (95% CI [-0.092 , 0.328]), respectively (FAS). Since the 95% CIs were contained within the equivalence margin of [-0.6 , 0.6], the change in DAS28 score was similar between the BRENZYS and Enbrel[®] treatment groups at Week 24 and at Week 52 (Table 9).

Table 7. ACR20 Response Rates; Per-protocol Set 1 (Study SB4-G31-RA)

ACR Response	Time Point	Treatment	n/n'	(%)	Adjusted Difference Rate	95% CI ^b
ACR20 ^a	Week 24	BREZYS 50 mg (N=247)	193/247	(78.1)	-2.37%	-9.54%, 4.80%
		Enbrel [®] 50 mg (N=236)	190/236	(80.5)		

^a ACR20: American College of Rheumatology 20% response criteria

^b Equivalence was declared if the 2-sided 95% confidence interval (CI) of the difference of the 2 proportions was entirely contained within the margin of [-15%, 15%].

CI: confidence interval; N: number of patients in the per-protocol set 1 (consisted of all full analysis patients who completed the Week 24 visit and had an adherence (from baseline to Week 24) within the range 80-120% of both the expected number of BREZYS or Enbrel[®] injections and the expected sum of MTX doses without any major protocol deviations (PDs) that affected the efficacy assessment. The PPS1 was the primary analysis set); n': number of patients with an assessment; n: number of responders.

Table 8. ACR 20/50/70 Response Rates; Full Analysis Set (Study SB4-G31-RA)

ACR Response	Time Point	Treatment	n/n'	(%)	Adjusted Difference Rate	95% CI
ACR20 ^a	Week 24	BREZYS 50 mg (N=299)	220/299	(73.6)	1.66%	-5.50%, 8.82%
		Enbrel [®] 50 mg (N=297)	213/297	(71.7)		
	Week 52	BREZYS 50 mg (N=299)	210/299	(70.2)	4.48%	-2.90%, 11.87%
		Enbrel [®] 50 mg (N=297)	195/297	(65.7)		
ACR50 ^b	Week 24	BREZYS 50 mg (N=299)	128/299	(42.8)	3.84%	-3.91%, 11.60%
		Enbrel [®] 50 mg (N=297)	116/297	(39.1)		
	Week 52	BREZYS 50 mg (N=299)	143/299	(47.8)	5.48%	-2.32%, 13.29%
		Enbrel [®] 50 mg (N=297)	125/297	(42.1)		
ACR70 ^c	Week 24	BREZYS 50 mg (N=299)	69/299	(23.1)	3.25%	-3.20%, 9.70%
		Enbrel [®] 50 mg (N=297)	59/297	(19.9)		
	Week 52	BREZYS 50 mg (N=299)	91/299	(30.4)	5.90%	-1.12%, 12.93%
		Enbrel [®] 50 mg (N=297)	73/297	(24.6)		

^a ACR20: American College of Rheumatology 20% response criteria

^b ACR50: American College of Rheumatology 50% response criteria

^c ACR70: American College of Rheumatology 70% response criteria

CI: confidence interval; N: number of patients in the full analysis set (consisted of all subjects who were randomized at the randomisation visit); n': number of patients with an assessment; n: number of responders. Patients with missing ACR20/50/70 responses were considered as non-responders at Week 24 and/or Week 52.

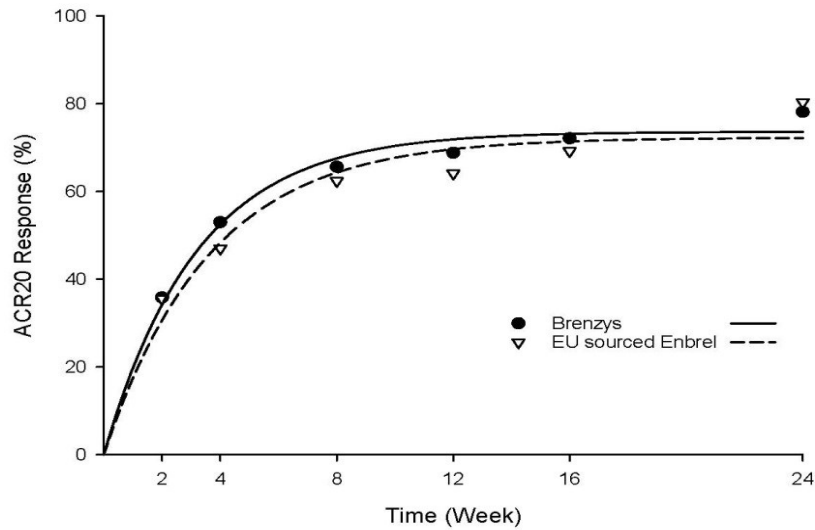


Figure 2. Time-Response Model for ACR20 Response up to Week 24 (Per-protocol Set 1) (Study SB4-G31-RA)

The major clinical response rate (maintenance of an ACR70 response over a 6-consecutive month period) at Week 52 for FAS was 20.8% (54/259) in the BRENZYS patients and 18.3% (45/246) in Enbrel[®] patients. The result was comparable between the BRENZYS and Enbrel[®] treatment groups.

The results of other efficacy endpoints are presented in Table 9.

Table 9. Outcomes from Other Secondary Efficacy Endpoints; Full Analysis Set (Study SB4-G31-RA)

Parameter	Time Point	Treatment	n	Difference in LSMeans	95% CI
Change in DAS28 ^a	Week 24	BRENZYS 50 mg (N=299)	287	0.072	-0.135, 0.279 ^c
		Enbrel [®] 50 mg (N=297)	272		
	Week 52	BRENZYS 50 mg (N=299)	287	0.118	-0.092, 0.328 ^c
		Enbrel [®] 50 mg (N=297)	272		
mTSS ^b	Week 52	BRENZYS 50 mg (N=299)	250	-0.27	-0.80, 0.26
		Enbrel [®] 50 mg (N=297)	228		

^a DAS28: Disease Activity Score based on a 28-joint count

^b mTSS: Change from baseline in modified Total Sharp Score

^c Equivalence was declared if the 2-sided 95% confidence interval (CI) of the difference of the 2 proportions was entirely contained within the margin of [-0.6 to 0.6].

CI: confidence interval; N: number of patients in the full analysis set (consisted of all subjects who were randomized at the randomisation visit); n: number of patients with available assessment results

Physical Function Response

The physical function of the subject was assessed using the Health Assessment

Questionnaire-Disability Index (HAQ-DI). It assessed the degree of difficulty a person has had in accomplishing tasks in eight functional areas over the previous 7 days, taking into account any aids or help required. The test results at baseline and Week 52 are listed in Table 10.

Table 10. Summary of Physical Function Test Results at Baseline and Week 52; Full Analysis Set (Study SB4-G31-RA)

HAQ-DI (0-3)	BRENZYS 50 mg (N=299)	Enbrel [®] 50 mg (N=297)
Baseline		
n	298	297
Mean (SD)	1.4904 (0.55292)	1.5097 (0.55983)
Min, Max	0.000, 3.000	0.000, 2.875
Week 24		
n	287	272
Mean (SD)	0.8541 (0.60771)	0.8616 (0.60612)
Min, Max	0.000, 2.875	0.000, 2.750
Week 52		
n	259	246
Mean (SD)	0.7674 (0.59791)	0.7973 (0.65357)
Min, Max	0.000, 2.750	0.000, 2.625

HAQ-DI: Health Assessment Questionnaire-Disability Index; SD: standard deviation; Min: minimum; Max: maximum

Radiographic Response

In study SB4-G31-RA, the change in modified total sharp score (joint erosion score plus joint space narrowing score) was analysed using ANCOVA with treatment group and region as factors and baseline value as a covariate for the subjects who had completed the Week 52 visit.

The change from baseline in mean mTSS was comparable between the BRENZYS and Enbrel[®] treatment groups (0.45 and 0.74, respectively) at Week 52. The change from baseline in mean joint erosion score was 0.26 and 0.31 in the BRENZYS and Enbrel[®] treatment groups, respectively, and the change from baseline in mean joint space narrowing score was 0.18 and 0.43 in the BRENZYS and Enbrel[®] treatment groups, respectively.

The mean change in mTSS at Week 52 and 95% CI was -0.27 and (-0.80, 0.26).

A summary of structural joint damage assessment by visit and treatment group and the results for change from baseline in mTSS at Week 52 among the completers is presented in Table 11.

In addition, graphical presentation of the cumulative distribution of the change in mTSS is presented in Figure 3.

Table 11. Summary of Structural Joint Damage at Week 52; Full Analysis Set (Study SB4-G31-RA)

	BRENZYS 50 mg		Enbrel[®] 50 mg	
	N=299		N=297	
Modified total sharp score, mean (SD)				
n	250		228	
Week 0	43.26	(67.083)	38.88	(53.256)
Week 52	43.70	(67.081)	39.62	(53.414)
Change	0.45	(2.497)	0.74	(3.356)
Joint erosion score, mean (SD)				
n	250		228	
Week 0	24.01	(39.625)	20.52	(28.324)
Week 52	24.28	(39.547)	20.84	(28.391)
Change	0.26	(1.608)	0.31	(1.677)
Joint space narrowing score, mean (SD)				
n	250		228	
Week 0	19.24	(28.834)	18.35	(26.479)
Week 52	19.43	(28.936)	18.78	(26.550)
Change	0.18	(1.142)	0.43	(2.096)

n: number of completers with available radiographic assessment results at Week 0 and Week 52.

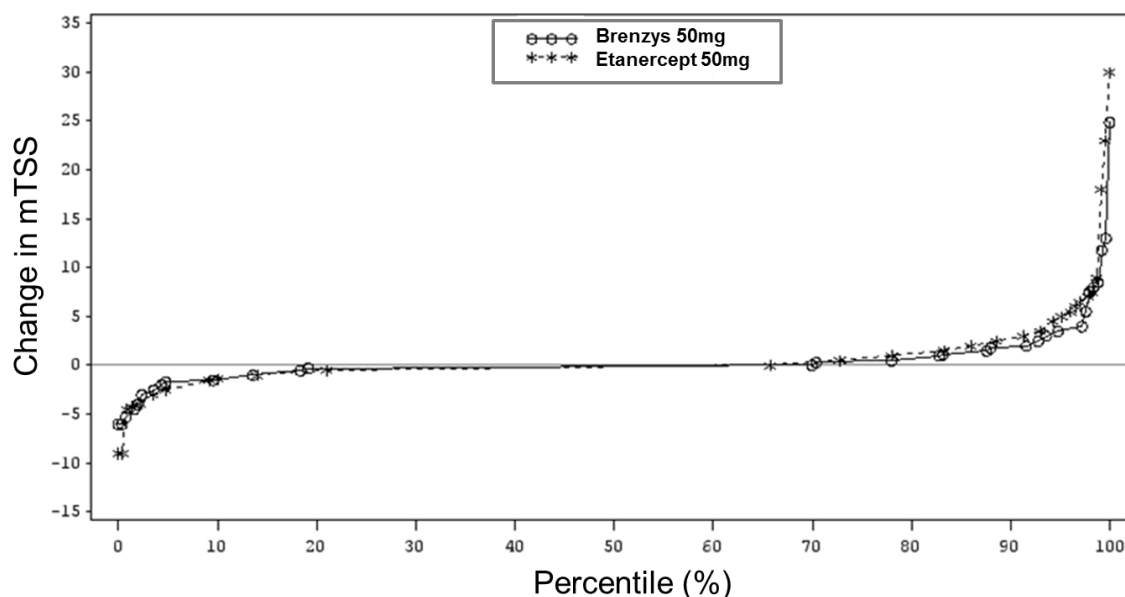


Figure 3. Summary Cumulative Distribution of the Change in mTSS at Week 52 (Study SB4-G31-RA)

Immunogenicity (Healthy Subject)

A total of 138 healthy subjects were enrolled and randomized in the clinical Phase I study SB4-G11-NHV, with 46 subjects in each of the three parts.

Blood samples were collected pre-dose and 4 weeks after the first injection of the study drugs for determination of ADAs and NAbs to etanercept (single doses of BRENZYS 50 mg SC, EU Enbrel[®] 50 mg SC, US Enbrel[®] 50 mg SC). The incidence of ADAs to etanercept and

NABs on Day 29 in each part of study SB4-G11-NHV in healthy subject is presented in Table 12.

Table 12. Incidence of Anti-Drug Antibodies to Etanercept and Neutralizing Antibodies on Day 29 (Safety Set) (Study SB4-G11-NHV)

	Treatment Group	
	BRENZYS N=23	EU Enbrel [®] N=23
	n/ n' (%)	n/ n' (%)
ADA		
Day 1 (baseline)		
Positive	0/23 (0.0)	0/23 (0.0)
Negative	23/23 (100.0)	23/23 (100.0)
Day 29		
Positive	0/22 (0.0)	3/23 (13.0)
Negative	22/22 (100.0)	20/23 (87.0)
NAb		
Day 1 (baseline)		
Positive	0/0 (0.0)	0/3 (0.0)
Negative	0/0 (0.0)	3/3 (100.0)
Day 29		
Positive	0/0 (0.0)	1/3 (33.3)
Negative	0/0 (0.0)	2/3 (66.7)

ADA: anti-drug antibody; NAb: neutralizing antibody; N: number of subjects in the safety set; n' is the number of subjects with available assessment at each visit.

Percentages for ADA result were based on only the number of subjects who were tested for ADA.

Percentages for NAb result were based on only the number of subjects with positive ADA.

NAb was assessed in subjects with ADA positive on Day 29. NAb positive was determined if Day 1 (baseline) NAb was negative and Day 29 NAb was positive. NAb negative was determined if both Day 1 (baseline) NAb and Day 29 NAb were negative or if Day 1 (baseline) NAb was positive (in spite of baseline ADA was negative) regardless of Day 29 NAb results.

Immunogenicity (RA)

A total of 596 patients with moderate to severe RA despite MTX therapy were randomized in a 1:1 ratio to receive either BRENZYS 50 mg (n=299) or Enbrel[®] 50 mg (n=297) once weekly for up to 52 weeks via self-administered SC injection. The immunogenicity analyses were performed using the safety set (n=596; BRENZYS: n=299; Enbrel[®]: n=297).

Blood samples for determination of immunogenicity were collected at baseline and Weeks 2, 4, 8, 12, 16, 24, and 52.

The incidence of ADAs and NABs to etanercept for the safety set is presented in

Table 13.

Table 13. Summary of Immunogenicity Testing (Safety Set) (Study SB4-G31-RA)

Timepoint	Parameter	Assessment	BRENZYS (N=299)			Enbrel® (N=297)			Total (N=596)		
			n'	n	(%)	n'	n	(%)	n'	n	(%)
Week 0 (Baseline)	ADA	Positive	299	0	0.0	297	0	(0.0)	596	0	(0.0)
		Negative	299	299	(100.0)	297	297	(100.0)	596	596	(100.0)
	NAb	Positive		0			0			0	
		Negative		0			0			0	
Week 4	ADA	Positive	299	1	(0.3)	291	32	(11.0)	590	33	(5.6)
		Negative	299	298	(99.7)	291	259	(89.0)	590	557	(94.4)
	NAb	Positive		0			1			1	
		Negative		1			31			32	
Week 8	ADA	Positive	298	1	(0.3)	288	6	(2.1)	586	7	(1.2)
		Negative	298	297	(99.7)	288	282	(97.9)	586	579	(98.8)
	NAb	Positive		0			0			0	
		Negative		1			6			7	
Week 12	ADA	Positive	294	0	0.0	280	1	(0.4)	574	1	(0.2)
		Negative	294	294	(100)	280	279	(99.6)	574	573	(99.8)
	NAb	Positive		0			0			0	
		Negative		0			1			1	
Week 16	ADA	Positive	290	0	0.0	277	0	(0.0)	567	0	(0.0)
		Negative	290	290	(100.0)	277	277	(100.0)	567	567	(100.0)
	NAb	Positive		0			0			0	
		Negative		0			0			0	
Week 24	ADA	Positive	288	0	0.0	272	0	(0.0)	560	0	(0.0)
		Negative	288	288	(100.0)	272	272	(100.0)	560	560	(100.0)
	NAb	Positive		0			0			0	
		Negative		0			0			0	
Week 52	ADA	Positive	260	1	(0.4)	246	0	(0.0)	506	1	(0.2)
		Negative	260	259	(99.6)	246	246	(100.0)	506	505	(99.8)
	NAb	Positive		0			0			0	
		Negative		1			0			1	
Week 52 overall*	ADA	Positive	299	3	(1.0)	296	39	(13.2)	595	42	(7.1)
		Negative	299	296	(99.0)	296	257	(86.8)	595	553	(92.9)
	NAb	Positive		0			1			1	
		Negative		3			38			41	

ADA: anti-drug antibody; NAb: neutralizing antibody.

n': number of subjects with available ADA results against BRENZYS or Enbrel® at each timepoint.

Percentages were based on n'.

NAb results only for subjects with ADA positive against BRENZYS or Enbrel® were used for the summary.

*: Overall ADA results at Week 8, Week 24 and Week 52 were determined as "Positive" if at least one ADA positive until the timepoint regardless the ADA result at Week 0 and "Negative" if no ADA positive until the timepoint regardless the ADA result at Week 0.

Adult Ankylosing Spondylitis

Randomized clinical trials have not been conducted to compare BRENZYS to Enbrel® in patients with adult ankylosing spondylitis. Clinical efficacy and safety studies have been conducted in patients with rheumatoid arthritis to demonstrate clinical comparability between BRENZYS and Enbrel®. The extrapolation of these data to support uses of BRENZYS in adult ankylosing spondylitis is based on the demonstrated comparability, in terms of product quality, non-clinical, human pharmacokinetic and clinical characteristics.

DETAILED PHARMACOLOGY

Since BRENZYS is a Subsequent Entry Biologic, where the pharmacodynamic and pharmacokinetic properties of etanercept have already been described for the reference product, Enbrel[®], this section summarizes the extensive comparative studies that were conducted to compare the pharmacology of BRENZYS to Enbrel[®].

Pharmacodynamics

Comparative *in vitro* studies including the evaluation of TNF receptor related biological activities and Fc related binding characteristics were performed to demonstrate comparability between BRENZYS and Enbrel[®].

An *in vivo* study to demonstrate comparable suppressive activity of BRENZYS and Enbrel[®] on TNF- α mediated pathology in a mouse (BALB/c) model of collagen antibody-induced arthritis (CAIA) was also performed. In this study, BRENZYS and Enbrel[®] suppressed the development of arthritis which was determined by footpad volume changes, clinical scores, and histopathological evaluation. No significant differences were detected among BRENZYS and Enbrel[®] treated groups.

In vitro Studies

Comparative *in vitro* studies were conducted to evaluate comparability between BRENZYS and Enbrel[®].

The relevant assays were qualified and closely associated with the mode of action of etanercept (TNF- α , LT- α 3 binding assay and NF- κ B reporter gene assay). Fc related binding and functional activities were assessed as well, although the main function of the Fc region in etanercept is to prolong half-life rather than to impart on Fc mediated effector activity.

An overview of the *in vitro* studies conducted comparing BRENZYS (clinical batches, and PVR batches) to Enbrel[®] is given in Table 14.

Table 14. Overview of Studies Comparing *In vitro* Activity between BRENZYS and Enbrel[®]

Type	Assay	Results for Comparability Assessments
Fab related biological activities (qualified assays)	TNF- α binding assay	Within the comparability range (91-112%)
	LT- α 3 binding assay	Within the comparability range (87-116%)
	TNF- α neutralization assay by NF- κ B reporter gene	Within the comparability range (81-133%)
Fc related biological activities	Fc γ RIa binding assay	3 out of 11 values (122%, 122%, 123%) were slightly out of the comparability range (90-121%)
	Fc γ RIIa binding assay	Within the comparability range (2.10E-06 to 4.94E-06)
	Fc γ RIIb binding assay	Within the comparability range (1.81E-05 to 3.35E-05)
	Fc γ RIIIa binding assay (V type)	Within the comparability range (2.50E-06 to 4.09E-06)

	FcRn assay	Within the comparability range (4.80E-06 to 1.18E-05)
Biological activities: additional assays	Binding assay to TNF- α from different species	Similar based on side-by-side qualitative evaluation
	Fc γ RIIIa binding assay (F type)	
	Fc γ RIIIb binding assay	
	C1q binding assay	
	Apoptosis assay	
	CDC assay	
	ADCC assay	

The comparability range was set by statistical analysis based on the tolerance interval (mean \pm κ SD using two-tiered tolerance limit) with the given set of available data points (Howe, 1969).

In terms of comparability, all *in vitro* studies results were within the comparability range, with the exception of Fc γ RIa. The binding activity of one clinical batch and two PVR batches of BRENZYS drug product were found to be slightly higher than the upper limit of the comparability range. However, the difference was minor (1-2%), and was considered to be within assay variability (intermediate precision from qualification studies: 5.7%).

Overall, the binding activity to Fc γ RIa is known to be associated with ADCC activity. As ADCC is not a mode of action of etanercept, the differences in Fc γ RIa are not considered to be important based on the known pharmacodynamics. Subsequent studies evaluating the ADCC activity of BRENZYS and Enbrel[®] confirmed the absence of ADCC activity in both BRENZYS and Enbrel[®].

In summary, the overall results of the *in vitro* assays associated with the mechanism of action of etanercept and Fc related binding assays demonstrated comparability between BRENZYS and Enbrel[®].

***In vivo* Studies**

ArthritoMab[™], a cocktail of monoclonal antibodies targeting the C11b, J1, D3, and U1 epitopes was employed for the induction of CAIA. These epitopes are spread across the CB8, CB10, and CB11 fragments of the type II collagen molecule, allowing good immune complex formation. The severity and incidence of the disease was increased by a subsequent lipopolysaccharide (LPS) challenge. To induce arthritis, each mouse (BALB/c; female) received 2 mg (0.2 mL) of ArthritoMab[™] via tail vein injection on Day 1 of the study. On Day 7, each animal was challenged with an intraperitoneal (IP) injection of 50 μ g (0.2 mL) LPS.

On Day 8, footpad volumes were measured with a paw volume plethysmograph system (Kent Scientific Corporation, Torrington, CT, USA). The mice were sorted into treatment cohorts such that there were no significant differences among the group mean total footpad volumes. On Day 8, all mean total footpad volumes were either 0.38 or 0.39 mL.

Table 15. Overview of the Pharmacodynamic Programme

Study Type	Route of Administration	Species	Dose (mg/kg/day)	Test Article	Dosing Frequency	GLP	Study Number
<i>In vivo</i> efficacy study	Intraperitoneal injection	BALB/c mice (collagen-antibody induced arthritis model)	1, 5, 10	BRENZYS EU Enbrel® US Enbrel®	Once daily at three-day intervals for five doses (Days 8, 12, 15, 19 and 22)	No	CAIA-e007

Nine treatment groups of mice (10 animals/group) were administered with BRENZYS, EU Enbrel®, or US Enbrel® at doses of 1, 5, and 10 mg/kg on Days 8, 12, 15, 19, and 22. The control group received vehicle only.

Plethysmometric right and left hind paw footpad volumes, and the sums of clinical scores – visible redness and/or swelling for all four paws (0–15 points/paw) determined on Day 8 (baseline) were reassessed on Days 9, 11, 12, 13, 15, 19, and 22. After the mice were euthanised on Day 22, formalin-fixed left hind limbs were evaluated for histopathological changes.

Efficacy was determined from the decreases in volume changes (disease burden and disease suppression) and clinical scores, and the increased incidence of animals with lower composite histopathology scores, relative to the vehicle treated controls.

All test articles suppressed the development of arthritis which was determined by changes in footpad volumes and clinical scores. Footpad volumes significantly reduced in all treated groups with no significant differences among treated groups. The results from clinical scores evaluation and the histopathological evaluation indicated a lesser destruction of joint architecture in all treated groups.

In summary, the suppressive activity of BRENZYS in BALB/c mice is considered comparable to that of Enbrel®.

TOXICOLOGY

BRENZYS is a SEB where the animal toxicology properties of etanercept have already been characterized for the reference product Enbrel®. This section summarizes the comparative toxicity studies that were conducted to compare BRENZYS to Enbrel®.

A 4-week comparative repeat-dose toxicity study in cynomolgus monkeys was conducted to demonstrate comparability in toxicity, toxicokinetic profiles, and immunogenicity profiles of BRENZYS and Enbrel®.

The overview of the toxicology programme is shown in Table 16. Local tolerance and potential immunotoxicity were examined as part of the 4-week repeat-dose toxicity study.

Table 16. Overview of the Toxicology Programme

Study Type	Route of Administration	Species	Dose (mg/kg/day)	Test Article	Dosing Frequency	GLP	Study Number
4-week comparative repeat-dose toxicity study	Subcutaneous bolus injection	Cynomolgus Monkey	0, 1, 15	BRENZYS EU Enbrel [®] US Enbrel [®]	Twice weekly	Yes	2064-004

BRENZYS, EU Enbrel[®], and US Enbrel[®] were well tolerated up to 15 mg/kg/day in the majority of animals with no remarkable findings and the toxicity, toxicokinetic, and immunogenicity profile of BRENZYS were comparable to those of Enbrel[®].

Consistent with information available for previous non-clinical studies with Enbrel[®], no test article-related effects were observed on mean body weight, ECG, pathology parameters, and ophthalmoscopic examination.

In addition, there were no test article-related effects on the mean numbers of peripheral blood leukocyte subtypes, except one animal given 15 mg/kg/day of BRENZYS (animal number 409) which had a significant decrease in the number of peripheral blood leukocytes at study termination.

There were no significant macroscopic or microscopic findings, or organ weight changes attributed to BRENZYS or Enbrel[®] except for the following.

- In the group receiving 1 mg/kg/day of US Enbrel[®], one male animal (number 439) required early study termination on Day 17 due to severe clinical signs such as lethargy and breathing difficulties. Microscopic evaluation revealed acute/chronic inflammation/adhesion of the pericardium and heart. Histological staining indicated the presence of bacterial colonies. This infection was likely to be a pre-existing condition and the immunosuppressive effect of etanercept may have contributed to the severity of the bacterial infection.
- In the group receiving 15 mg/kg/day of BRENZYS, one male animal (number 409) had microscopic changes in the incidence of macrophages mainly in the spleen and liver which was attributed to the immunosuppressive effect of etanercept in an animal with pre-existing subclinical endogenous infection.

Regarding anti-drug antibody (ADA) formation, all animals treated with low dose (1 mg/kg/day) showed a positive response from Day 22 to study termination. The ADA response was less prevalent in the high dose (15 mg/kg/day) group with no significant differences between BRENZYS and Enbrel[®] suggesting that the decreased ADA response in the animals that received the high dose might be caused by drug interference due to the high concentration of test articles.

In the toxicokinetic evaluation, mean C_{max} and AUC was generally increased in proportion to the dose of BRENZYS and Enbrel[®]. In addition, no significant differences were observed in mean serum concentrations, C_{max} and AUC on Day 1 and Day 25 between the treatment groups (Table 17).

Table 17. Pharmacokinetic Parameters in Cynomolgus Monkeys Following Subcutaneous Administration of Repeat Doses of BRENZYS or Enbrel®

Type of Study	Species	Daily Doses mg/kg	Test Article	C _{max} (µg/mL)				AUC _(0-last) (µg·hr/mL)			
				Day 1		Day 25		Day 1		Day 25	
				M	F	M	F	M	F	M	F
4-week repeat-dose toxicity study	Cynomolgus Monkey	1	BRENZYS	12.7	11.0	5.07	0.662	755	621	271	17.5
			EU Enbrel®	11.7	50.1 13.0 ^b	2.49	0.303	639	1420 719 ^b	83.6	10.7
			US Enbrel®	11.1	12.3	2.0 ^c	0.494	649	739	61.2 ^c	14.6
		15	BRENZYS	173	148	229	192	10200	9080	13400	11100
			EU Enbrel®	145 125 ^a	152	213	44.6	7180 7170 ^a	9570	11700	1940
			US Enbrel®	179	148	232	122	11300	8780	12500	6020

M: Male, F: Female

^a Value excluding data for animal 415.

^b Value excluding data for animal 412.

^c Value excluding data for animal 439, which was euthanized *in extremis* on Day 17.

Overall, the results of Study 2064-004 showed that the toxicity, toxicokinetic, and immunogenicity profiles of BRENZYS were comparable to those of Enbrel®.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

BRENZYS (pronounced) <BREN-ziss>

etanercept

Single-use Pre-filled Syringe

Read this carefully before you start taking BRENZYS and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about BRENZYS.

BRENZYS is a subsequent entry biologic (SEB) to Enbrel[®]. An SEB is a biologic drug product that is authorized based on its likeness to a biologic drug product already authorized for sale in Canada. This leaflet is a summary and will not tell you everything about BRENZYS. Contact your doctor or pharmacist if you have any questions about the drug.

Serious Warnings and Precautions

- **Serious infections.** There have been cases where patients taking BRENZYS or other TNF-blocking agents have developed serious infections, including tuberculosis (TB) and infections caused by bacteria, viruses or fungi that have spread throughout their body. Some patients have died from these infections. In very rare cases, hepatitis B recurred in patients with previous hepatitis. If you tend to get infections easily or if you develop an infection while taking BRENZYS, you should tell your doctor right away.
- **Malignancies.** BRENZYS is not indicated for use in children less than 18 years of age; however, there have been cases, sometimes fatal, of unusual cancers in children and teenage patients who started using TNF-blocking agents, including etanercept, at less than 18 years of age.

What is BRENZYS used for?

BRENZYS is a medicine for treating people with moderate to severe forms of rheumatoid arthritis (RA). BRENZYS is also for treating adults with a type of arthritis called ankylosing spondylitis (ank-e-low-sing spond-e-lie-tis (AS). RA, and AS are inflammatory diseases that affect the joints in your body.

How does BRENZYS work?

BRENZYS is a type of protein called a tumour necrosis factor (TNF) blocker that blocks the action of a substance your body makes called TNF-alpha. TNF-alpha is made by your body's immune system. People with immune diseases like RA as well as patients with AS, have too much TNF-alpha in their bodies, which can cause inflammation and lead to painful, swollen joints. BRENZYS can reduce the amount of TNF in the body to normal levels, helping to treat joint damage. In patients with inflammatory arthritis, BRENZYS may be effective in reducing signs and symptoms of inflammatory arthritis (such as pain, morning stiffness and fatigue), may help improve your ability to do simple daily activities (such as dressing, walking and climbing stairs), and may help prevent damage to your bones and joints.

What are the ingredients in BRENZYS?

Medicinal ingredients: etanercept

Non-medicinal ingredients: Sodium chloride, Sodium phosphate and Sucrose

BRENZYS comes in the following dosage forms:

BRENZYS single-use pre-filled syringes are available as a 50 mg dosage strength (0.98 mL of a 50 mg/mL solution of etanercept, minimum deliverable volume of 0.94 mL).

BRENZYS single-use pre-filled auto-injectors are available as a 50 mg dosage strength (0.98 mL of a 50 mg/mL solution of etanercept, minimum deliverable volume of 0.93 mL).

Do not use BRENZYS if:

- you have ever had an allergic reaction to BRENZYS or any of the ingredients in BRENZYS.
- you have, or are at risk of developing a serious blood infection called sepsis.
- you have an infection of any kind.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take BRENZYS. Talk about any health conditions or problems you may have, including if you:

- have an infection. This could put you at risk for serious side effects from BRENZYS.
- have symptoms of an infection such as fever, sweats or chills, cough or flu-like symptoms, shortness of breath, blood in your phlegm, weight loss, muscle aches, warm, red, or painful areas on your skin, sores on your body, diarrhea or stomach pain, burning when you urinate or urinate more often than normal, and feel very tired.
- have a history of infections that keep coming back or other conditions — like diabetes, HIV, or a weak immune system — that might increase your risk of infections.
- have tuberculosis (TB), or have been in close contact with someone who has or has had TB. You will need to be evaluated for TB. Your doctor should test you for TB before starting BRENZYS.
- were born in, lived in, or traveled to countries where there is a risk for getting TB. Ask your doctor if you are not sure.
- live in, have lived in or have traveled to, areas where there is a greater risk for certain kinds of fungal infections (histoplasmosis, coccidioidomycosis, blastomycosis). These infections may develop or become more severe if you take BRENZYS. If you don't know if you have lived in an area where these infections are common, ask your doctor.
- have or have had hepatitis B.
- have or have had persistent numbness, tingling and muscle weakness or a disease such as multiple sclerosis, Guillain- Barré or a Guillain-Barré -like syndrome, which causes inflammation of the nervous system, either in the brain and spinal cord or nerves going to your hands and feet.
- have been newly diagnosed or are being treated for congestive heart failure.
- are scheduled to have major surgery.
- have recently received or are scheduled to receive a vaccine. All vaccines should be brought up-to-date before starting BRENZYS. Patients taking BRENZYS should not receive live vaccines.

- use the medication Kineret[®] (anakinra), Orencia[®] (abatacept) or cyclophosphamide (see “The following may interact with BRENZYS:” below).
- have been around someone with varicella zoster (chicken pox, shingles).

Your doctor should monitor you closely for signs and symptoms of TB during treatment with BRENZYS even if you have tested negative for TB. If you develop any of the symptoms of TB (a dry cough that doesn't go away, weight loss, fever, night sweats) call your doctor.

Other warnings you should know about:

All medicines have side effects. Medicines, like BRENZYS, that affect your immune system can cause serious side effects. The possible serious side effects include:

- **Nervous system diseases.** There have been rare cases of disorders that affect the nervous system of people taking BRENZYS or other TNF blockers, such as multiple sclerosis, seizures or inflammation of the nerves of the eyes. Signs that you could be experiencing a problem affecting your nervous system include: numbness or tingling throughout your body, problems with your vision, weakness in your arms and/or legs, and dizziness.
- **Blood problems.** In some patients the body may fail to produce enough of the blood cells that can help your body fight infections or help you to stop bleeding. This can lead to death. If you develop a fever that doesn't go away, bruise or bleed very easily or look very pale or feel faint, call your doctor right away. Your doctor may decide to stop treatment. Some people have also had symptoms that resemble lupus (rash on your face and arms that gets worse in the sun) that may go away when you stop taking BRENZYS.
- **Heart problems.** You should also tell your doctor if you have ever been treated for heart failure. If you have, your doctor may choose not to start you on BRENZYS, or may want to monitor you more closely. Symptoms include shortness of breath or swelling of your ankles and feet.
- **Allergic reactions.** Some patients have had allergic reactions to BRENZYS. If you develop a severe rash, swollen face or difficulty breathing while taking BRENZYS, call your doctor right away.
- **Malignancies.** Patients with inflammatory diseases including RA or AS, particularly those with highly active disease, may be at higher risk for lymphoma (a type of cancer). For patients taking TNF-blocker medicines including BRENZYS, the chances of getting lymphoma or other cancers may increase. Whether treatment with BRENZYS might influence the development and course of malignancies in adults is unknown.
- **Liver problems (autoimmune hepatitis).** Liver problems can happen in people who use TNF blocker medicines, including BRENZYS. These problems can lead to liver failure and death. Call your doctor right away if you have any of these symptoms: feel very tired, skin or eyes look yellow, poor appetite or vomiting, pain on the right side of your stomach (abdomen). These symptoms may occur several months after starting and even after BRENZYS has been stopped.
- **Psoriasis.** Some people using BRENZYS developed new psoriasis or worsening of psoriasis they already had. Tell your doctor if you develop red scaly patches or raised bumps which may be filled with pus. Your doctor may decide to stop your treatment with BRENZYS.
- **Serious infections.** BRENZYS can lower the ability of your immune system to fight infections. So, taking BRENZYS can make you more prone to getting infections or make any infection that you may have worse. Some people have serious infections while taking BRENZYS including infections that spread through the body such as tuberculosis (TB),

legionellosis (usually a bacterial pneumonia), and listeriosis (usually from contaminated food). Other infections caused by viruses, fungi, bacteria or parasites may occur. Some people have died from these infections.

What are the common side effects?

In studies comparing etanercept to placebo (inactive injection), side effects that occurred more frequently in patients treated with etanercept were:

- Reactions where the injection was given. These reactions are usually mild and include redness, swelling, itching, or bruising. These usually go away within 3 to 5 days. If you have pain, redness or swelling around the injection site that doesn't go away or gets worse, call your doctor.
- Upper respiratory infections (sinus infections)
- Headaches

When can I expect to see results from taking BRENZYS?

Improvement may be seen as early as 1 week after starting etanercept in adults. In clinical trials, full effect was usually seen by 3 months in adults and was sustained with continued treatment.

Can I take BRENZYS if I am pregnant or breastfeeding?

BRENZYS has not been studied in pregnant women or nursing mothers, therefore its effects on pregnant women or nursing babies are not known.

You should tell your doctor if you are pregnant, become pregnant or are thinking about becoming pregnant. If you took BRENZYS during pregnancy, talk to your doctor prior to administration of live vaccines to your infant.

BRENZYS can pass into breast milk. You and your doctor should decide if you will take BRENZYS or breastfeed. You should not do both.

If you are not sure or have any questions about any of this information, ask your doctor.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

In adults, BRENZYS can be used in combination with methotrexate.

The following may interact with BRENZYS:

- **Anakinra.** Taking BRENZYS with Kineret[®] (anakinra) is not recommended because this may increase your risk of getting a serious infection.
- **Abatacept.** Taking BRENZYS with Orencia[®] (abatacept) is not recommended because this may increase your risk for serious side effects.
- **Cyclophosphamide.** Taking BRENZYS with cyclophosphamide (used to treat cancer or immune diseases) is not recommended. You may have a higher chance for getting certain cancers when taking BRENZYS with cyclophosphamide.

If you have diabetes and are taking medication to control your diabetes, your doctor may decide you need less anti-diabetic medicine while taking BRENZYS.

How to take BRENZYS:

BRENZYS is administered by an injection under the skin.

You may continue to use other medicines that help treat your condition while taking BRENZYS, such as non-steroidal anti-inflammatory drugs (NSAIDs) and prescription steroids, as recommended by your doctor.

Detailed instructions on how to inject BRENZYS are provided in “Instructions for Use”. Do not mix the BRENZYS solution with any other medicine.

To help you remember, it may be helpful to write in a diary which day(s) of the week BRENZYS should be used.

Usual dose:

Rheumatoid arthritis (RA) or ankylosing spondylitis (AS)

The usual dose is 50 mg once a week as an injection under the skin. However, your doctor may determine an alternative frequency at which to inject BRENZYS.

Your doctor will decide how long you should take BRENZYS and whether retreatment is needed based on your response. If BRENZYS has no effect on your condition after 12 weeks, your doctor may tell you to stop taking this medicine.

Overdose:

If you accidentally inject BRENZYS more frequently than instructed, talk to a doctor or pharmacist immediately.

If you think you have taken too much BRENZYS, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take BRENZYS when you are supposed to, contact your doctor to find out when to take your next dose of BRENZYS.

What are possible side effects from using BRENZYS?

These are not all the possible side effects you may feel when taking BRENZYS. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

Like all medicines, BRENZYS can cause side effects. Most side effects are mild to moderate. However, some may be serious and require treatment.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON Injection site reactions		✓	
COMMON Upper respiratory tract infections (sinus infections)		✓	
Headaches	✓		
RARE Serious infections		✓	✓
Tuberculosis		✓	
Nerve disorders		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at [MedEffet](#);
- By calling 1-866-234-2345 (toll-free);
- By completing a Patient Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada, Postal Locator 0701E
Ottawa, ON
K1A 0K9

Postage paid labels and the Patient Side Effect Reporting Form are available at [MedEffet](#).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

The BRENZYS pre-filled syringe should be refrigerated at 2°C to 8°C. **Do NOT freeze BRENZYS.** Refrigerated BRENZYS remains stable until the expiration date printed on the syringe.

BRENZYS may be transferred to room temperature storage (up to 27°C). Upon removal from the refrigerator, it must be used within 60 days. Protect from direct sunlight, sources of heat, and humidity until ready to use.

Keep out of reach and sight of children.

If you want more information about BRENZYS:

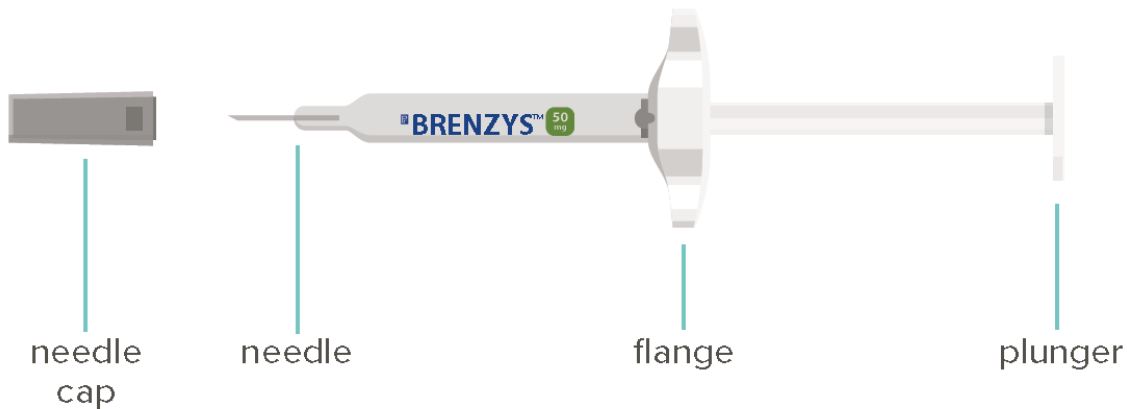
- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website](#); the Canadian distributor (Merck Canada Inc.)’s website www.merck.ca, or by calling 1-800-567-2594.

This information is current up to the last revision date shown below, but more current information may be available from the manufacturer.

Instructions for Use:

The following instructions are for preparing and giving a dose of BRENZYS using a single-use pre-filled syringe.

Your pre-filled syringe:



Step 1: Gather supplies

- Place your syringe and unopened alcohol swabs on a clean, dry surface.
- Remember to wash your hands.
- Don't uncap.



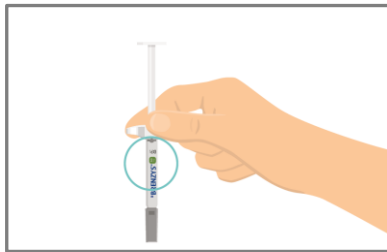
Step 2: Wait 30 minutes

- Wait approximately 30 minutes for your syringe to warm-up to room temperature, which helps reduce your pain during injection.
- Don't remove the cap just yet.



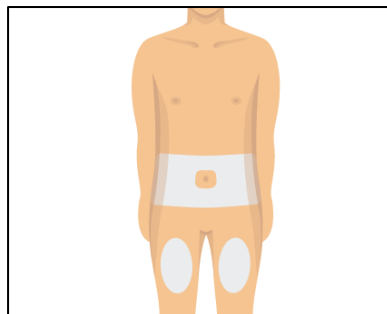
Step 3: Inspect medicine & date

- Always make sure your medicine hasn't expired.
- The medicine should be clear and colorless, and may contain small particles.
- You may see an air bubble, and that's okay.
- Don't remove the cap just yet.



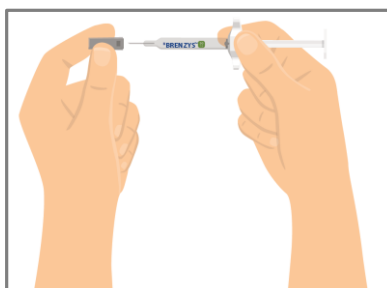
Step 4: Choose site & clean skin

- Choose an injection site on your body.
- Your abdomen or thighs are best.
- Wipe your skin at the injection site with an alcohol swab.
- Avoid skin that's sore, bruised, scarred, scaly or has red patches.



Step 5: Remove syringe cap

- Carefully remove the needle cap.



Step 6: Pinch skin & insert needle

- Gently pinch your skin, and carefully insert the needle.



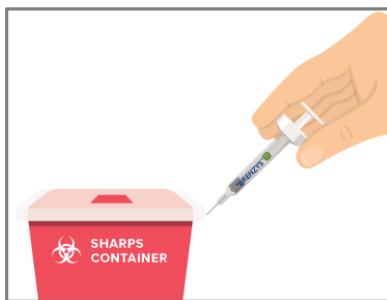
Step 7: Push plunger all the way

- Hold the syringe steady and press the plunger all the way down.



Step 8: Remove syringe & dispose

- Pull the syringe away from your skin and dispose of it in a sharps container.
- Don't recap or reuse your needle.



This leaflet was prepared by Samsung Bioepis Co., Ltd.

Last Revised <MON-DD-YYYY>

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

BRENZYS (pronounced) <BREN-ziss>

etanercept

Single-use Pre-filled Auto-injector

Read this carefully before you start taking BRENZYS and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about BRENZYS.

BRENZYS is a subsequent entry biologic (SEB) to Enbrel[®]. An SEB is a biologic drug product that is authorized based on its likeness to a biologic drug product already authorized for sale in Canada. This leaflet is a summary and will not tell you everything about BRENZYS. Contact your doctor or pharmacist if you have any questions about the drug.

Serious Warnings and Precautions

- **Serious infections.** There have been cases where patients taking BRENZYS or other TNF-blocking agents have developed serious infections, including tuberculosis (TB) and infections caused by bacteria, viruses or fungi that have spread throughout their body. Some patients have died from these infections. In very rare cases, hepatitis B recurred in patients with previous hepatitis. If you tend to get infections easily or if you develop an infection while taking BRENZYS, you should tell your doctor right away.
- **Malignancies.** BRENZYS is not indicated for use in children less than 18 years of age; however, there have been cases, sometimes fatal, of unusual cancers in children and teenage patients who started using TNF-blocking agents, including etanercept, at less than 18 years of age.

What is BRENZYS used for?

BRENZYS is a medicine for treating people with moderate to severe forms of rheumatoid arthritis (RA). BRENZYS is also for treating adults with a type of arthritis called ankylosing spondylitis (ank-e-low-sing spond-e-lie-tis (AS). RA and AS are inflammatory diseases that affect the joints in your body.

How does BRENZYS work?

BRENZYS is a type of protein called a tumour necrosis factor (TNF) blocker that blocks the action of a substance your body makes called TNF-alpha. TNF-alpha is made by your body's immune system. People with immune diseases like RA, as well as patients with AS, have too much TNF-alpha in their bodies, which can cause inflammation and lead to painful, swollen joints. BRENZYS can reduce the amount of TNF in the body to normal levels, helping to treat joint damage. In patients with inflammatory arthritis, BRENZYS may be effective in reducing signs and symptoms of inflammatory arthritis (such as pain, morning stiffness and fatigue), may help improve your ability to do simple daily activities (such as dressing, walking and climbing stairs), and may help prevent damage to your bones and joints.

What are the ingredients in BRENZYS?

Medicinal ingredients: etanercept

Non-medicinal ingredients: Sodium chloride, Sodium phosphate and Sucrose

BRENZYS comes in the following dosage forms:

BRENZYS single-use pre-filled syringes are available as a 50 mg dosage strength (0.98 mL of a 50 mg/mL solution of etanercept, minimum deliverable volume of 0.94 mL).

BRENZYS single-use pre-filled auto-injectors are available as a 50 mg dosage strength (0.98 mL of a 50 mg/mL solution of etanercept, minimum deliverable volume of 0.93 mL).

Do not use BRENZYS if:

- you have ever had an allergic reaction to BRENZYS or any of the ingredients in BRENZYS.
- you have, or are at risk of developing a serious blood infection called sepsis.
- you have an infection of any kind.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take BRENZYS. Talk about any health conditions or problems you may have, including if you:

- have an infection. This could put you at risk for serious side effects from BRENZYS.
- have symptoms of an infection such as fever, sweats or chills, cough or flu-like symptoms, shortness of breath, blood in your phlegm, weight loss, muscle aches, warm, red, or painful areas on your skin, sores on your body, diarrhea or stomach pain, burning when you urinate or urinate more often than normal, and feel very tired.
- have a history of infections that keep coming back or other conditions — like diabetes, HIV, or a weak immune system — that might increase your risk of infections.
- have tuberculosis (TB), or have been in close contact with someone who has or has had TB. You will need to be evaluated for TB. Your doctor should test you for TB before starting BRENZYS.
- were born in, lived in, or traveled to countries where there is a risk for getting TB. Ask your doctor if you are not sure.
- live in, have lived in or have traveled to, areas where there is a greater risk for certain kinds of fungal infections (histoplasmosis, coccidioidomycosis, blastomycosis). These infections may develop or become more severe if you take BRENZYS. If you don't know if you have lived in an area where these infections are common, ask your doctor.
- have or have had hepatitis B.
- have or have had persistent numbness, tingling and muscle weakness or a disease such as multiple sclerosis, Guillain- Barré or a Guillain-Barré -like syndrome, which causes inflammation of the nervous system, either in the brain and spinal cord or nerves going to your hands and feet.
- have been newly diagnosed or are being treated for congestive heart failure.
- are scheduled to have major surgery.
- have recently received or are scheduled to receive a vaccine. All vaccines should be brought up-to-date before starting BRENZYS. Patients taking BRENZYS should not receive live vaccines.

- use the medication Kineret[®] (anakinra), Orencia[®] (abatacept) or cyclophosphamide (see “The following may interact with BRENZYS:” below).
- have been around someone with varicella zoster (chicken pox, shingles).

Your doctor should monitor you closely for signs and symptoms of TB during treatment with BRENZYS even if you have tested negative for TB. If you develop any of the symptoms of TB (a dry cough that doesn’t go away, weight loss, fever, night sweats) call your doctor.

Other warnings you should know about:

All medicines have side effects. Medicines, like BRENZYS, that affect your immune system can cause serious side effects. The possible serious side effects include:

- **Nervous system diseases.** There have been rare cases of disorders that affect the nervous system of people taking BRENZYS or other TNF blockers, such as multiple sclerosis, seizures or inflammation of the nerves of the eyes. Signs that you could be experiencing a problem affecting your nervous system include: numbness or tingling throughout your body, problems with your vision, weakness in your arms and/or legs, and dizziness.
- **Blood problems.** In some patients the body may fail to produce enough of the blood cells that can help your body fight infections or help you to stop bleeding. This can lead to death. If you develop a fever that doesn’t go away, bruise or bleed very easily or look very pale or feel faint, call your doctor right away. Your doctor may decide to stop treatment. Some people have also had symptoms that resemble lupus (rash on your face and arms that gets worse in the sun) that may go away when you stop taking BRENZYS.
- **Heart problems.** You should also tell your doctor if you have ever been treated for heart failure. If you have, your doctor may choose not to start you on BRENZYS, or may want to monitor you more closely. Symptoms include shortness of breath or swelling of your ankles and feet.
- **Allergic reactions.** Some patients have had allergic reactions to BRENZYS. If you develop a severe rash, swollen face or difficulty breathing while taking BRENZYS, call your doctor right away.
- **Malignancies.** Patients with inflammatory diseases including RA or AS, particularly those with highly active disease, may be at higher risk for lymphoma (a type of cancer). For patients taking TNF-blocker medicines including BRENZYS, the chances of getting lymphoma or other cancers may increase. Whether treatment with BRENZYS might influence the development and course of malignancies in adults is unknown.
- **Liver problems (autoimmune hepatitis).** Liver problems can happen in people who use TNF blocker medicines, including BRENZYS. These problems can lead to liver failure and death. Call your doctor right away if you have any of these symptoms: feel very tired, skin or eyes look yellow, poor appetite or vomiting, pain on the right side of your stomach (abdomen). These symptoms may occur several months after starting and even after BRENZYS has been stopped.
- **Psoriasis.** Some people using BRENZYS developed new psoriasis or worsening of psoriasis they already had. Tell your doctor if you develop red scaly patches or raised bumps which may be filled with pus. Your doctor may decide to stop your treatment with BRENZYS.
- **Serious infections.** BRENZYS can lower the ability of your immune system to fight infections. So, taking BRENZYS can make you more prone to getting infections or make any infection that you may have worse. Some people have serious infections while taking

BRENZYS including infections that spread through the body such as tuberculosis (TB), legionellosis (usually a bacterial pneumonia), and listeriosis (usually from contaminated food). Other infections caused by viruses, fungi, bacteria or parasites may occur. Some people have died from these infections.

What are the common side effects?

In studies comparing etanercept to placebo (inactive injection), side effects that occurred more frequently in patients treated with etanercept were:

- Reactions where the injection was given. These reactions are usually mild and include redness, swelling, itching, or bruising. These usually go away within 3 to 5 days. If you have pain, redness or swelling around the injection site that doesn't go away or gets worse, call your doctor.
- Upper respiratory infections (sinus infections)
- Headaches

When can I expect to see results from taking BRENZYS?

Improvement may be seen as early as 1 week after starting etanercept in adults. In clinical trials, full effect was usually seen by 3 months in adults and was sustained with continued treatment.

Can I take BRENZYS if I am pregnant or breastfeeding?

BRENZYS has not been studied in pregnant women or nursing mothers, therefore its effects on pregnant women or nursing babies are not known.

You should tell your doctor if you are pregnant, become pregnant or are thinking about becoming pregnant. If you took BRENZYS during pregnancy, talk to your doctor prior to administration of live vaccines to your infant.

BRENZYS can pass into breast milk. You and your doctor should decide if you will take BRENZYS or breastfeed. You should not do both.

If you are not sure or have any questions about any of this information, ask your doctor.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

In adults, BRENZYS can be used in combination with methotrexate.

The following may interact with BRENZYS:

- **Anakinra.** Taking BRENZYS with Kineret[®] (anakinra) is not recommended because this may increase your risk of getting a serious infection.
- **Abatacept.** Taking BRENZYS with Orencia[®] (abatacept) is not recommended because this may increase your risk for serious side effects.
- **Cyclophosphamide.** Taking BRENZYS with cyclophosphamide (used to treat cancer or immune diseases) is not recommended. You may have a higher chance for getting certain cancers when taking BRENZYS with cyclophosphamide.

If you have diabetes and are taking medication to control your diabetes, your doctor may decide you need less anti-diabetic medicine while taking BRENZYS.

How to take BRENZYS:

BRENZYS is administered by an injection under the skin.

You may continue to use other medicines that help treat your condition while taking BRENZYS, such as non-steroidal anti-inflammatory drugs (NSAIDs) and prescription steroids, as recommended by your doctor.

Detailed instructions on how to inject BRENZYS are provided in “Instructions for Use”.

Do not mix the BRENZYS solution with any other medicine.

To help you remember, it may be helpful to write in a diary which day(s) of the week BRENZYS should be used.

Usual dose:

Rheumatoid arthritis (RA) or ankylosing spondylitis (AS)

The usual dose is 50 mg once a week as an injection under the skin.

However, your doctor may determine an alternative frequency at which to inject BRENZYS.

Your doctor will decide how long you should take BRENZYS and whether retreatment is needed based on your response. If BRENZYS has no effect on your condition after 12 weeks, your doctor may tell you to stop taking this medicine.

Overdose:

If you accidentally inject BRENZYS more frequently than instructed, talk to a doctor or pharmacist immediately.

If you think you have taken too much BRENZYS, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take BRENZYS when you are supposed to, contact your doctor to find out when to take your next dose of BRENZYS.

What are possible side effects from using BRENZYS?

These are not all the possible side effects you may feel when taking BRENZYS. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

Like all medicines, BRENZYS can cause side effects. Most side effects are mild to moderate. However, some may be serious and require treatment.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON Injection site reactions		✓	
COMMON Upper respiratory tract infections (sinus infections)		✓	
Headaches	✓		
RARE Serious infections		✓	✓
Tuberculosis		✓	
Nerve disorders		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at [MedEffet](#);
- By calling 1-866-234-2345 (toll-free);
- By completing a Patient Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada, Postal Locator 0701E
Ottawa, ON
K1A 0K9

Postage paid labels and the Patient Side Effect Reporting Form are available at [MedEffet](#).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

The BRENZYS pre-filled auto-injector should be refrigerated at 2°C to 8°C. **Do NOT freeze BRENZYS.** Refrigerated BRENZYS remains stable until the expiration date printed on the auto-injector.

BRENZYS may be transferred to room temperature storage (up to 27°C). Upon removal from the refrigerator, it must be used within 60 days. Protect from direct sunlight, sources of heat, and humidity until ready to use.

Keep out of reach and sight of children.

If you want more information about BRENZYS:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website](#); the Canadian distributor (Merck Canada Inc.)'s website www.merck.ca, or by calling 1-800-567-2594.

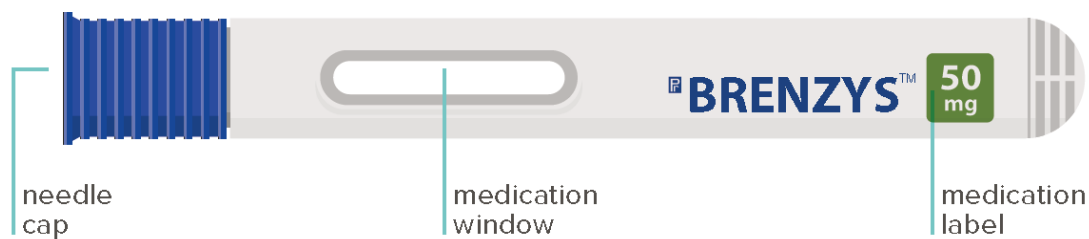
This information is current up to the last revision date shown below, but more current information may be available from the manufacturer.

Instructions for Use:

The following instructions are for preparing and giving a dose of BRENZYS using a single-use pre-filled auto-injector.

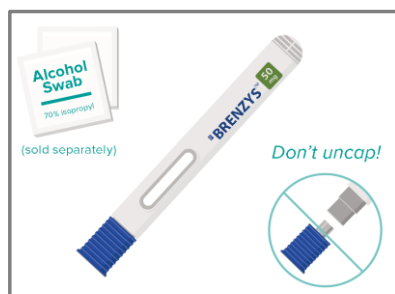
Your pre-filled auto-injector:

- There is no button on your auto-injector.
- The needle is hidden behind a shield, under the cap.
- When you push the shield onto your skin, the injection will start automatically.



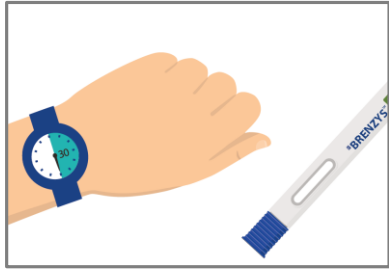
Step 1: Gather supplies

- Place your auto-injector and unopened alcohol swabs on a clean, dry surface.
- Remember to wash your hands.
- Don't uncap.



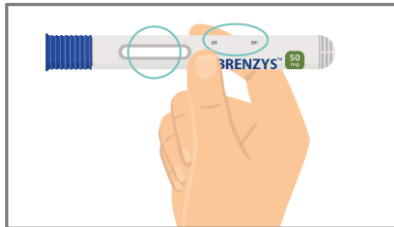
Step 2: Wait 30 minutes

- Wait approximately 30 minutes for your auto-injector to warm-up to room temperature, which helps reduce your pain during injection.
- Don't remove the cap just yet.



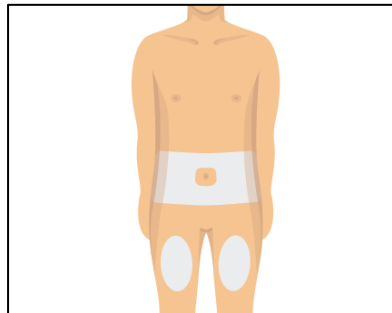
Step 3: Inspect medicine & date

- Always make sure your medicine hasn't expired.
- The medicine should be clear and colorless, and may contain small particles.
- You may see an air bubble, and that's okay.
- Don't remove the cap just yet.



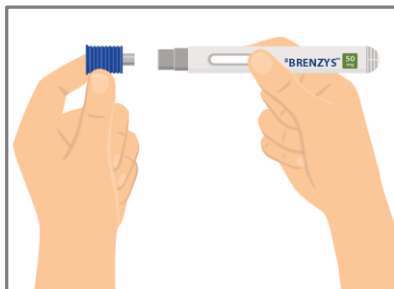
Step 4: Choose site & clean skin

- Choose an injection site on your body.
- Your abdomen or thighs are best.
- Wipe your skin at the injection site with an alcohol swab.
- Avoid skin that's sore, bruised, scarred, scaly or has red patches.



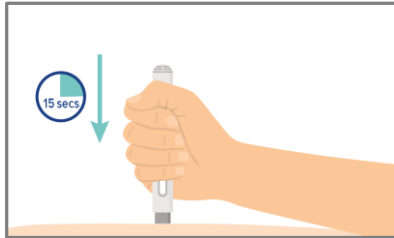
Step 5: Remove the blue needle cap

- Carefully remove the blue needle cap with a metal center from the auto-injector.



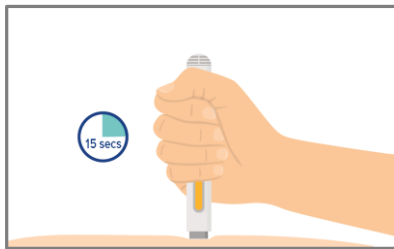
Step 6: Place gray needle shield, press down and hold 15 seconds

- Place the gray needle shield straight on your skin, and push the entire auto-injector down firmly to start the injection.
- When you push down, the injection starts.
- You may hear a click.



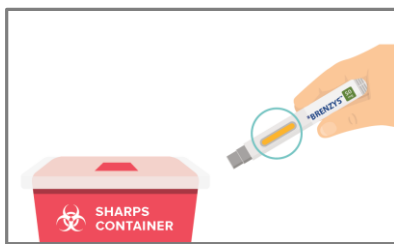
Step 7: After 15 seconds, remove auto-injector

- Hold the auto-injector against your skin.
- After 15 seconds, remove the auto-injector from the injection site.
- You may hear a second click.



Step 8: Confirm completion & dispose auto-injector

- Confirm that the entire medication window is yellow.
- Discard your auto-injector in a sharps container.
- If the entire window isn't yellow, you may not have received your full dose.



This leaflet was prepared by Samsung Bioepis Co., Ltd.

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