

AUSTRALIAN PRODUCT INFORMATION – BRENZYS® (ETANERCEPT) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Etanercept

Brenzys is a biosimilar medicine to Enbrel®. The evidence for comparability supports the use of Brenzys for the listed indication(s).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

50 mg solution for injection in pre-filled syringe

Each pre-filled syringe contains 50 mg of etanercept.

50 mg solution for injection in Auto-injector

Each Auto-injector contains 50 mg of etanercept.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Solution for injection (injection).

Brenzys solution for injection in the pre-filled syringe and in the Auto-injector is a clear, colourless or pale yellow solution with a pH of 6.2 ± 0.3 .

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Brenzys is indicated for the treatment of:

Adults (≥ 18 years)

Rheumatoid Arthritis

Active, adult rheumatoid arthritis (RA) in patients who have had inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs). Brenzys can be used in combination with methotrexate.

Severe, active rheumatoid arthritis in adults to slow progression of disease-associated structural damage in patients at high risk of erosive disease.

Psoriatic Arthritis

The signs and symptoms of active and progressive psoriatic arthritis in adults, when the response to previous disease-modifying antirheumatic therapy has been inadequate. Etanercept has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Plaque Psoriasis

Adult patients with moderate to severe chronic plaque psoriasis, who are candidates for phototherapy or systemic therapy.

Ankylosing Spondylitis

The signs and symptoms of active ankylosing spondylitis in adults.

Non-radiographic Axial Spondyloarthritis

Treatment of adults with active* non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or MRI change who have had an inadequate response to NSAIDs.

*Active disease is defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥ 4 .

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, or plaque psoriasis. Patients may self-inject only if their physician determines that it is appropriate and with medical follow-up, as necessary, after proper training in injection technique.

Adults (≥ 18 years)

Rheumatoid arthritis, psoriatic arthritis, non-radiographic axial spondyloarthritis and ankylosing spondylitis

The recommended dose of Brenzys is 50 mg administered once weekly, given as a subcutaneous injection.

Available data in non-radiographic axial spondyloarthritis suggest a clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

Plaque psoriasis

The recommended dose of Brenzys is 50 mg per week, given once weekly (single 50 mg injection) as a subcutaneous injection. Higher responses may be achieved from initial treatment for up to 12 weeks with a dose of 50 mg given twice weekly, after which, the dose should be reduced to the standard dose of 50 mg per week. Treatment should be discontinued in patients who do not show a significant PASI response after 12 weeks. If re-treatment with Brenzys is indicated, the dose used should be 50 mg per week.

Elderly patients

Elderly RA patients (age ≥ 65 years) show similar safety, efficacy and pharmacokinetic profiles compared to younger adult patients treated with etanercept. Dose adjustment is not needed for the elderly. However, as with other medicinal products, greater sensitivity in some older patients cannot be ruled out.

Children and adolescents

Brenzys is not indicated for use in children less than 18 years of age, since Brenzys is only presented as a 50 mg pre-filled syringe and 50 mg pre-filled auto-injector. Brenzys is not available in a 25 mg strength.

Other etanercept products with appropriate dosage forms for children are available.

Instructions for use, handling and disposal

Before injecting

Sites for self-injection include thigh, abdomen or upper arm. Injection sites should be rotated. New injections should be given at least 3 cm from an old site and never into areas where the skin is tender, bruised, red or hard (see “Instructions for Use” supplied with Brenzys).

Pre-filled syringe (Solution for injection): Before injecting, Brenzys single-use pre-filled syringes should be allowed to reach room temperature (approximately 30 minutes). The needle cover should not be removed during this period. The solution should be clear, colourless or pale yellow and practically free from visible particles. Otherwise, do not inject the solution. Use a different Brenzys pre-filled syringe, then contact your pharmacist for assistance.

Auto-injector (Solution for injection): Before injecting, Brenzys single-use Auto-injector should be allowed to reach room temperature (approximately 30 minutes). Immediate use is then recommended. The needle cover should not be removed while allowing the Auto-injector to reach room temperature. By looking through the inspection window, the solution should be clear and colourless or pale yellow and practically free from visible particles. Otherwise, do not inject the solution. Use a different Brenzys Auto-injector, then contact your pharmacist for assistance.

Brenzys is for single use only. Any unused product should be disposed of appropriately.

Administration

If a patient is to self-administer Brenzys, they should be instructed in injection techniques to ensure the safe self-administration of Brenzys (See “Instructions for Use” supplied with Brenzys). The first injection should be performed under the supervision of a qualified health care professional. The ability of that patient to self-inject subcutaneously should be assessed. A puncture-resistant container for disposal of syringes should be used. Patients should be instructed in the technique and told the importance of proper syringe disposal and be cautioned against reuse of these items.

Disposal

Contains no antimicrobial agent. Product is for single use only in one patient only. Discard any residue.

4.3 CONTRAINDICATIONS

Known hypersensitivity to etanercept or to any of its excipients.

Patients with, or at risk of, sepsis.

Treatment with Brenzys should not be initiated in patients with serious, active infection including chronic or localised infections.

Concurrent treatment with Interleukin-1 antagonists.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The comparability of Brenzys with Enbrel® has been demonstrated, with regard to physicochemical characteristics and efficacy and safety outcomes (see Section 5 PHARMACOLOGICAL PROPERTIES and Section 4.1 THERAPEUTIC INDICATION). The level of comparability that has been shown supports the use of Brenzys for the listed indications.

Traceability

In order to improve the traceability of biological medicines, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Infections

Patients should be evaluated for infections before, during and after treatment with Brenzys, taking into consideration that the mean elimination half-life of etanercept is 80 hours (standard deviation of 28 hours; range from 7 to 300 hours).

Serious infections including sepsis and tuberculosis, have been reported with the use of etanercept (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Some of these infections have been fatal. These infections were due to bacteria, mycobacteria, fungi, viruses and parasites (including protozoa). Opportunistic infections have also been reported (including listeriosis, legionellosis and invasive fungal infections) in patients receiving etanercept. Many of these serious events have occurred in patients receiving concomitant medicines including immunosuppressants, or with underlying diseases that, in addition to their RA, could predispose them to infections. In some cases, fungal and other opportunistic infections are not recognised and this has resulted in delays in appropriate treatment, sometimes resulting in death. Patients who develop a new infection while undergoing treatment with etanercept should be monitored closely. Administration of etanercept should be discontinued if a patient develops a serious infection (e.g., tuberculosis or an atypical mycobacterial infection) or sepsis.

In evaluating patients for infections, physicians should consider the patient's risk for relevant opportunistic infections (e.g., exposure to endemic mycoses). Physicians should exercise caution when considering the use of etanercept in patients with a history of recurring or chronic infections or with underlying conditions, which may predispose patients to infections such as advanced or poorly controlled diabetes (see Section 4.3 CONTRAINDICATIONS). Caution should be exercised in patients at high risk of developing serious infection, including patients undergoing major surgery.

Tuberculosis (TB)

Tuberculosis (including disseminated or extrapulmonary presentation) has been observed in patients receiving TNF-blocking agents, including etanercept. Tuberculosis may be due to reactivation of latent TB infection or to new infection. Before initiation of therapy with etanercept, any patient at increased risk for TB should be evaluated for active or latent infection. If active TB is diagnosed, Brenzys therapy must not be initiated. Prophylaxis of latent TB infection should be initiated prior to therapy with Brenzys. Treatment of latent TB in patients with a reactive tuberculin test reduces the risk of TB reactivation in patients receiving TNF blockers. Some patients who tested negative for latent TB prior to receiving etanercept have developed active TB. Physicians should monitor patients receiving Brenzys for signs and symptoms of active TB, including patients who tested negative for latent TB infection. Applicable local guidelines should be consulted. Patients with RA appear to have an increased rate of TB infection. Cases of TB and atypical mycobacterial infections including *Mycobacterium avium* complex in patients on treatment with etanercept have been reported. Treatment should be ceased immediately if mycobacterial infection is suspected. All patients should be informed to seek medical advice if signs/symptoms suggestive of TB (e.g., persistent cough, wasting/weight loss, low grade fever) appear during or after Brenzys treatment.

Reactivation of hepatitis B

Reactivation of hepatitis B in patients who were previously infected with the hepatitis B virus (HBV) and had received TNF blockers, including etanercept, has been reported. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients at risk for HBV infection should be evaluated for evidence of prior HBV infection before initiating TNF blocker therapy. Prescribers should exercise caution in prescribing TNF blockers for patients previously infected with HBV. Patients who were previously infected with HBV and require treatment with TNF blockers should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of

therapy. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. If HBV reactivation should develop in patients who are receiving Brenzys, treatment should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Worsening of hepatitis C

There have been reports of worsening of hepatitis C in patients receiving etanercept, although a causal relationship with etanercept has not been established.

Alcoholic hepatitis

In a study of 48 hospitalised patients treated with etanercept or placebo for moderate to severe alcoholic hepatitis, Etanercept was not efficacious and the mortality rate in patients treated with etanercept was significantly higher after 6 months. Infections were also higher in the etanercept group. The use of Brenzys in patients for the treatment of alcoholic hepatitis is not recommended. Physicians should use caution when using Brenzys in patients who also have moderate to severe alcoholic hepatitis.

Hypoglycaemia in patients treated for diabetes

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

Inflammatory bowel disease (IBD) and uveitis in patients with juvenile idiopathic arthritis (JIA)

Brenzys is not indicated for use in children less than 18 years of age. There have been reports of IBD in JIA patients being treated with etanercept, which is not effective for the treatment of IBD. A causal relationship with etanercept is unclear because clinical manifestations of bowel inflammation have also been observed in untreated JIA patients. There have also been reports of uveitis in JIA patients being treated with etanercept.

Concurrent administration of TNF inhibitors and anakinra

Concurrent administration of etanercept and anakinra (a recombinant, non-glycosylated form of the human Interleukin-1 receptor antagonist) has been associated with an increased risk of serious infection, an increased risk of neutropenia and no additional benefit compared to etanercept alone. The safety and efficacy of anakinra used in combination with etanercept has not been established. Therefore, combination of etanercept and anakinra is contraindicated (see also Section 4.3 CONTRAINDICATIONS and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Concurrent administration of etanercept and abatacept

In clinical studies, concurrent administration of abatacept and etanercept therapy resulted in increased incidences of serious adverse events, including infections. This combination has not demonstrated increased clinical benefit; such use is not recommended (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Interstitial lung disease

There have been postmarketing reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes.

Haematological reactions

Rare cases of pancytopenia and very rare cases of aplastic anaemia, some with fatal outcome, have been reported in patients treated with etanercept. Caution should be exercised in patients being treated with Brenzys who have a previous history of blood dyscrasias. All patients should be advised that if they develop signs and symptoms suggestive of blood dyscrasias or infections

(eg, persistent fever, sore throat, bruising, bleeding, paleness) whilst on Brenzys, they should seek immediate medical advice. Such patients should be evaluated urgently, including full blood count; if any blood dyscrasias are confirmed, Brenzys should be discontinued.

Allergic reactions

Parenteral administration of any biological product should be attended by appropriate precautions in case an allergic or untoward reaction occurs. Allergic reactions associated with etanercept administration have been reported commonly. Allergic reactions have included angioedema and urticaria. Serious reactions have occurred (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). If any serious allergic or anaphylactic reaction occurs, Brenzys therapy should be discontinued immediately and appropriate therapy initiated.

Congestive heart failure

There have been post-marketing reports of worsening of congestive heart failure (CHF), with and without identifiable precipitating factors, in patients taking etanercept. There have also been rare (< 0.1%) reports of new onset CHF, including CHF in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. Two large clinical trials evaluating the use of etanercept in the treatment of CHF were terminated early due to lack of efficacy. Although not conclusive, data from one of these trials suggests a possible tendency towards worsening CHF and higher mortality in those patients assigned to etanercept treatment. Physicians should use caution when using Brenzys in patients who also have CHF and monitor patients carefully.

Neurological disorders

Although no clinical trials have been performed evaluating etanercept therapy in patients with multiple sclerosis, clinical trials of other TNF antagonists in patients with multiple sclerosis have shown increases in disease activity. Treatment with etanercept and other agents that inhibit TNF have been associated with rare cases of new onset or exacerbation of central nervous system demyelinating disorders, some presenting with mental status changes and some associated with permanent disability. Cases of transverse myelitis, optic neuritis, multiple sclerosis, and new onset or exacerbation of seizure disorders have been observed in association with etanercept therapy (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Additionally, there have been very rare reports of peripheral demyelinating polyneuropathies (including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy). A careful risk/benefit evaluation, including a neurological assessment, is recommended when prescribing Brenzys therapy to patients with pre-existing or recent onset of central nervous system (CNS) demyelinating disease, or to those who are considered to have an increased risk of developing demyelinating disease.

Use in psoriasis

There are limited data on the use of etanercept in combination with methotrexate for the treatment of psoriasis. The safety and efficacy of this combination in psoriasis have not been established.

The safety and efficacy of etanercept in combination with other immunosuppressive agents used in psoriasis or with phototherapy have not been studied. Brenzys should not be used in combination with such agents because of the possibility of excessive immunosuppression.

Monitoring

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

Carcinogenicity

Lymphomas

TNF modulates immune responses and has a protective effect against the development of some tumours. The impact of treatment with etanercept, on the course of development of malignancies, including those caused by immunosuppressive agents, is not understood and has not been studied. The possibility exists for anti-tumour necrosis factor (TNF) therapies, including etanercept, to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. The impact of treatment with etanercept on the development and course of malignancies and active and/or chronic infections is not fully understood (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Reports of malignancies affecting various sites have been received in the post-marketing period including breast and lung carcinoma and lymphoma.

In the controlled portions of clinical trials of all the TNF blocking agents, more cases of lymphoma have been observed among patients receiving the TNF blocker compared to control patients. During the controlled portions of etanercept trials, 3 lymphomas were observed among 4,509 etanercept-treated patients versus 0 among 2,040 control patients (duration of controlled treatment ranged from 3 to 24 months).

Among 6,543 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 U.S. population based on the Surveillance, Epidemiology, and End Results (SEER) Database. While patients with rheumatoid arthritis or psoriasis, particularly those with highly active disease, may be at a higher risk (up to several fold) for the development of lymphoma, a possible risk for the development of lymphomas or other malignancies in patients treated with a TNF-antagonist cannot be excluded.

Among 4,410 adult PsO patients treated with etanercept in clinical trials up to 36 months, representing approximately 4,278 patient-years of therapy, the observed rate of lymphoma was 0.05 cases per 100 patient-years, which is comparable to the rate in the general population. No cases were observed in etanercept- or placebo-treated patients during the controlled portions of these trials.

Leukaemia

Cases of acute and chronic leukaemia 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 leukaemia.

During the controlled portions of etanercept trials, 2 cases of leukaemia were observed among 5,445 (0.06 cases per 100 patient-years) etanercept-treated patients versus 0 among 2,890 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 leukaemia was 0.03 cases per 100 patient-years.

Other malignancies

Information is available from 10,953 adult patients with 17,123 patient-years and 696 paediatric patients with 1,282 patient-years of experience across 45 etanercept clinical studies.

For malignancies other than lymphoma and non-melanoma skin cancer, there was no difference in exposure adjusted rates between the 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 U.S. population based on the SEER database and suggests no increase in rates over time. Whether treatment with etanercept might influence the development and course of malignancies in adults is unknown.

Wegener's granulomatosis

In a placebo-controlled study of 180 patients with Wegener's granulomatosis, the addition of etanercept to standard treatment (including cyclophosphamide and high-dose steroids) was no more efficacious than standard treatment alone. The group of patients who received etanercept experienced more non-cutaneous malignancies of various types than the patient group receiving standard treatment alone. The use of Brenzys for treatment of Wegener's granulomatosis is not recommended.

Melanoma and non-melanoma skin cancer

Melanoma and non-melanoma skin cancer (NMSC) have been reported in patients treated with TNF-antagonists including etanercept. Postmarketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with etanercept. Periodic skin examination is recommended for all patients who are at increased risk for skin cancer. Combining the results of controlled portions of clinical trials of etanercept, more cases of non-melanoma skin cancer were observed in patients taking etanercept compared with control patients, particularly in patients with psoriasis. Long-term animal studies have not been conducted to evaluate the carcinogenic potential of etanercept.

Among 3,306 adult rheumatology (RA, PsA, AS) patients treated with etanercept in controlled clinical trials representing approximately 2,669 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 1,521 control-treated patients representing 1,077 patient-years. Among 1,245 adult psoriasis patients treated with etanercept in controlled clinical trials, representing approximately 283 patient-years of therapy, the observed rate of NMSC was 3.54 cases per 100 patient-years vs 1.28 cases per 100 patient-years among 720 control-treated patients representing 156 patient-years.

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.

Immunosuppression

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 safety and efficacy of etanercept, in patients with immunosuppression or chronic infections have not been evaluated.

Vaccinations

Most psoriatic patients receiving etanercept were able to mount an 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. Live vaccines should not be given concurrently with Brenzys (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). No data are available on the secondary transmission of infection by live vaccines in patients receiving etanercept. Patients with a significant exposure to varicella virus should temporarily discontinue Brenzys therapy and be considered for prophylactic treatment with varicella zoster immune globulin.

Brenzys is not indicated for use in children less than 18 years of age. Available data for etanercept treatment in the paediatric population is summarised below:

If possible, bring paediatric patients up to date with all immunisations (including varicella) in agreement with current immunisation guidelines prior to initiating etanercept therapy.

Autoantibody formation

Treatment with etanercept may result in the formation of autoimmune antibodies (see Section **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**). Rare reports have been described in clinical trials and post-marketing experience of autoimmune hepatitis, a lupus-like syndrome or rashes compatible with subacute cutaneous lupus or discoid lupus. If a patient develops symptoms and findings suggestive of autoimmune hepatitis or a lupus-like syndrome, treatment should be discontinued and the patient carefully evaluated.

Use in the elderly

A total of 480 RA patients aged 65 years or older have been studied in clinical trials. In PsO randomised clinical trials, a total of 138 out of 1,965 patients treated with etanercept or placebo were age 65 or older. No overall differences in safety or effectiveness were observed between these patients and younger patients, but the number of geriatric PsO patients is too small to determine whether they respond differently from younger patients. The clinical trial in non-radiographic axial spondyloarthritis did not include patients aged 50 years or older. Greater sensitivity of some older individuals cannot be ruled out. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

Paediatric use

Brenzys is not indicated for use in children less than 18 years of age. Available data for etanercept treatment in the paediatric population is summarised below:

Etanercept has not been studied in children less than 2 years of age. Studies have not been done in patients with juvenile idiopathic arthritis (JIA) to assess the effects of continued etanercept therapy in patients who do not respond within 3 months of initiating etanercept therapy. Additionally, studies have not been conducted to assess the effects of discontinuing or reducing the recommended dose of etanercept following its long-term use in patients with JIA.

Malignancies, some fatal, have been reported among children, adolescents and young adults who received treatment with TNF-blocking agents (initiation of therapy at \leq 18 years of age), including etanercept to treat JIA and other indications. Approximately half of the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were derived from several sources including registries and post-marketing reports. In addition, there was one case of lymphoma reported in paediatric clinical trials.

Two JIA patients developed varicella infection and signs and symptoms of aseptic meningitis, which resolved without sequelae. Patients with a significant exposure to varicella virus should temporarily discontinue etanercept therapy and be considered for prophylactic treatment with varicella zoster immune globulin.

There have been reports of inflammatory bowel disease and uveitis in patients with JIA (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE-Inflammatory bowel disease (IBD) and uveitis in patients with juvenile idiopathic arthritis (JIA)).

The long-term effects of etanercept on the growth and development of children are not known.

Effects on laboratory tests

No effects on laboratory tests have been reported in adults. An analysis of 54 JIA patients in an open-label study demonstrated low haemoglobin, low albumin and low lymphocyte counts in

63%, 39% and 30% of juvenile patients, respectively. These observations, however, appear to be attributed to the underlying disease, rather than treatment with etanercept.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Methotrexate

Brenzys may be administered in combination with methotrexate for the treatment of rheumatoid arthritis. In a safety and efficacy trial, methotrexate had no effect on the pharmacokinetics of etanercept. The effect of etanercept on the pharmacokinetics of methotrexate has not been investigated. Product Information for methotrexate should be consulted when Brenzys is administered with methotrexate.

Abatacept

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

Anakinra

Patients treated with etanercept and anakinra were observed to have a higher rate of serious infection (7%) when compared with patients who were treated with etanercept alone (0%, historical data). In addition, in a double-blind placebo-controlled trial, in patients receiving background methotrexate, patients treated with etanercept and anakinra were observed to have a higher rate of serious infection and neutropenia than patients who were treated with etanercept alone (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Cyclophosphamide

The use of Brenzys in patients receiving concurrent cyclophosphamide therapy is not recommended (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE-Other malignancies).

Live vaccines

No safety data are available on the effects of live vaccine when used in combination with etanercept. Live vaccines should therefore not be given concurrently with Brenzys.

Sulfasalazine

In a clinical study of patients who were receiving established doses of sulfasalazine, to which etanercept was added, patients in the combination group experienced a statistically significant decrease in mean white blood cell counts in comparison to groups treated with etanercept or sulfasalazine alone.

Digoxin

Etanercept does not significantly affect digoxin exposure. There was a reduction in etanercept exposure in the presence of digoxin, however there was significant inter-subject variability. The clinical significance of this reduced exposure is uncertain.

Table 1. Effect of Digoxin on Pharmacokinetic Parameters of Etanercept

Mean (SD)	Etanercept	Etanercept + Digoxin
C _{max} (µg/mL)	2.64 (1.24)	2.53 (1.93)
AUC _(0-t) (µg/mL·h)	152 (68.7)	133 (96.3)

Warfarin

Etanercept does not significantly affect warfarin exposure. There was a slight reduction in etanercept exposure in the presence of warfarin, however there was significant inter-subject variability. The clinical significance of this reduced exposure is uncertain.

Table 2. Effect of Warfarin on Pharmacokinetic Parameters of Etanercept

Mean (SD)	Etanercept	Etanercept +Warfarin
C _{max} (µg/mL)	3.5 (1.09)	3.09 (1.22)
AUC _(0-t) (µg/mL·h)	180 (71.9)	160 (75.1)

Other

In clinical trials, no apparent interactions have been observed when etanercept was administered with glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs) or analgesics.

4.6 FERTILITY, PREGNANCY AND LACTATION**Effects on fertility**

Long-term animal studies have not been conducted to evaluate the effects of etanercept on fertility.

Use in pregnancy – Pregnancy Category D

The safe use of etanercept during pregnancy has not been established. Therefore, Brenzys should be used during pregnancy only if clearly needed. Women of childbearing potential should be advised to use appropriate contraception to avoid becoming pregnant during Brenzys therapy and for three weeks after discontinuation of therapy.

Developmental toxicity studies have been performed in rats and rabbits at doses resulting in AUC-based systemic exposure levels of etanercept that were at least 12-fold higher than in humans at the highest proposed therapeutic dose of 50 mg and have revealed no evidence of harm to the fetus due to etanercept. There are, however, no studies in pregnant women. Animal studies are not always predictive of human response.

Etanercept crosses the placenta and has been detected in the serum of infants born to female patients treated with etanercept during pregnancy. The clinical impact of this is unknown, however, infants may be at increased risk of infection. Administration of live vaccines to infants for 16 weeks after the mother's last dose of Brenzys is generally not recommended.

A pregnancy registry examined the risk of major birth defects and other pregnancy outcomes in mothers with rheumatic diseases or psoriasis exposed to etanercept in the first trimester (n = 319) versus those who were unexposed to etanercept or other TNF-antagonists (n = 144). The all inclusive odds ratio for major birth defects in those exposed to etanercept was 2.77 (95% CI 1.04-7.35) compared to non-exposed mothers with inflammatory disease. The findings showed no clear pattern of major or minor malformations. There was no increase in rates of intrauterine or postnatal growth deficits or delayed postnatal development. The use of etanercept should be avoided during pregnancy. If Brenzys is used during pregnancy, or if the patient becomes pregnant while taking it, the woman should be advised of the possible risk to the fetus.

Use in lactation

The safe use of etanercept during lactation has not been established. Etanercept has been reported to be excreted in human breast milk following subcutaneous administration. There are no animal studies assessing the effects of etanercept on the neonate. Because of the potential for serious adverse reactions from etanercept in nursing infants, a decision should be made whether to discontinue nursing or to discontinue Brenzys while nursing.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

Injection site reactions

Patients with rheumatic diseases in controlled trials treated with etanercept had a significantly higher incidence (37% cf. 10%) of injection site reactions (erythema and/or itching, pain, bleeding, bruising or swelling) compared with placebo-treated patients, and generally did not necessitate drug discontinuation. The frequency of injection site reactions was greatest in the first month and subsequently decreased in frequency. Mean duration was 3 to 5 days. No treatment was given for the majority of injection site reactions in the etanercept treatment groups, and the majority of those patients who were given treatment received topical preparations such as corticosteroids, or oral antihistamines. Some patients who experienced injection site reactions also experienced reactions at previous injection sites. In post-marketing experience, injection site bleeding and bruising have also been observed in conjunction with etanercept therapy.

In controlled trials in patients with plaque psoriasis, approximately 13.6% of patients treated with etanercept developed injection site reactions compared with 3.4% of placebo-treated patients during the first 12 weeks of treatment.

Infections

In placebo-controlled trials, no increase in the incidence of serious infections (fatal, life-threatening, or requiring hospitalisation or intravenous antibiotics) was observed. Serious infections occurred in 6.3% of rheumatoid arthritis patients treated with etanercept for up to 48 months. These included abscess (at various sites), bacteraemia, bronchitis, bursitis, cellulitis, cholecystitis, diarrhoea, diverticulitis, endocarditis (suspected), gastroenteritis, hepatitis B, herpes zoster, leg ulcer, mouth infection, osteomyelitis, otitis, peritonitis, pneumonia, pyelonephritis, sepsis, septic arthritis, sinusitis, skin infection, skin ulcer, urinary tract infection, vasculitis, and wound infection. In the 2-year active-controlled study where patients were treated with either etanercept alone, methotrexate alone or etanercept in combination with methotrexate, the rates of serious infections were similar among the treatment groups. However, it cannot be excluded that the combination of etanercept with methotrexate could be associated with an increase in the rate of infections.

There were no differences in rates of infection among patients treated with etanercept and those treated with placebo for plaque psoriasis in placebo-controlled trials of up to 24 weeks duration. Serious infections experienced by etanercept-treated patients included cellulitis, gastroenteritis, pneumonia, cholecystitis, osteomyelitis, gastritis, appendicitis, Streptococcal fasciitis, myositis, septic shock, diverticulitis and abscess. In the double-blind and open-label psoriatic arthritis trials, 1 patient reported a serious infection (pneumonia).

Serious and fatal infections have been reported during use of etanercept; reported pathogens include bacteria, mycobacteria (including tuberculosis), viruses and fungi. Some have occurred within a few weeks after initiating treatment with etanercept in patients who have underlying conditions (e.g., diabetes, congestive heart failure, history of active or chronic infections) in addition to their rheumatoid arthritis. etanercept treatment may increase mortality in patients with established sepsis.

Opportunistic infections have been reported in association with etanercept, including invasive fungal, parasitic (including protozoal), viral (including herpes zoster), bacterial (including

Listeria and Legionella), and atypical mycobacterial infections (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). In a pooled data set of clinical trials, the overall incidence of opportunistic infections was 0.09% for the 15,402 subjects who received etanercept. The exposure-adjusted rate was 0.06 events per 100 patient-years. In postmarketing experience, approximately half of all of the case reports of opportunistic infections worldwide were invasive fungal infections. The most commonly reported invasive fungal infections included *Candida*, *Pneumocystis*, *Aspergillus* and *Histoplasma*. Invasive fungal infections accounted for more than half of the fatalities amongst patients who developed opportunistic infections. The majority of the reports with a fatal outcome were in patients with *Pneumocystis pneumonia*, unspecified systemic fungal infections, and aspergillosis.

Malignancies and lymphoproliferative disorders

Reports of malignancies affecting various sites have been received in the post-marketing period. The observed rates and incidences of new malignancies in clinical trials with etanercept were similar to those expected for the population studied. Patients have been observed in clinical trials with etanercept for over five years. Among 4,462 rheumatoid arthritis patients treated with etanercept in clinical trials for a mean of 27 months (approximately 10,000 patient-years of therapy), 9 lymphomas were observed for a rate of 0.09 cases per 100 patient-years. This is 3-fold higher than the rate of lymphomas expected in the general population based on the Surveillance, Epidemiology and End Results Database. An increased rate of lymphoma up to several fold has been reported in the rheumatoid arthritis patient population and may be further increased in patients with more severe disease activity (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE-Carcinogenicity).

There have been reports of malignancies in a clinical trial of patients being treated for Wegener's granulomatosis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE-Carcinogenicity).

Interstitial lung disease

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

Elevated liver enzymes

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

Autoimmune hepatitis

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

Autoantibody formation

In controlled trials, the percentage of patients who developed new positive antinuclear antibodies (ANA) ($\geq 1:40$), new positive anti-double-stranded DNA antibodies and new anticardiolipin antibodies were increased compared to placebo-treated patients (11% cf. 5%

respectively). 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.

Rare reports have been described in clinical trials and post-marketing experience, including patients with rheumatoid factor positive RA, who have developed additional antibodies in conjunction with autoimmune hepatitis, a lupus-like syndrome or rashes compatible with subacute cutaneous lupus or discoid lupus by clinical presentation and biopsy (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)-Other adverse reactions). The impact of long-term treatment with etanercept on the development of autoimmune diseases is unknown. If a patient develops symptoms and findings suggestive of a lupus-like syndrome or autoimmune hepatitis following treatment with etanercept, treatment should be discontinued and the patient should be carefully evaluated.

Psoriasis

Cases of new onset psoriasis, including pustular psoriasis and palmoplantar psoriasis, and cases of exacerbation of pre-existing psoriasis have been reported with the use of TNF blockers, including etanercept. Many of these patients were taking concomitant immunosuppressants (e.g., methotrexate, corticosteroids). Some of these patients required hospitalisation. Most patients had improvements of their psoriasis following discontinuation of their TNF blocker. Some patients have had recurrences of the psoriasis when they were re-challenged with a different TNF blocker. Discontinuation of Brenzys should be considered for severe cases and those that do not improve or that worsen despite topical treatments.

Other adverse reactions

Events reported in at least 3% of all patients with higher incidence in patients treated with etanercept compared to controls in placebo-controlled RA trials (including the combination methotrexate trial) and events per patient year are summarised in the next table.

Table 3. Percent of Rheumatoid Arthritis Patients Reporting Adverse Events and Events per Patient Year in Placebo-Controlled Clinical Trials^a

Event	Percent of Patients		Event per Patient Year	
	Placebo (n = 152)	Etanercept (n = 349)	Placebo (40 pt. years)	Etanercept (117 pt. years)
Injection site reaction	10	37	0.62	7.73
Infection	32	35	1.86	1.82
Non-upper respiratory infection ^b	32	38	1.54	1.50
Upper respiratory infection ^b	16	29	0.68	0.82
Headache	13	17	0.62	0.68
Rhinitis	8	12	0.35	0.45
Dizziness	5	7	0.25	0.21
Pharyngitis	5	7	0.17	0.24
Cough	3	6	0.17	0.18
Asthenia	3	5	0.10	0.16
Pain, Abdomen	3	5	0.12	0.17
Rash	3	5	0.12	0.21
Respiratory disorder	1	5	0.05	0.17
Dyspepsia	1	4	0.05	0.12

Event	Percent of Patients		Event per Patient Year	
	Placebo (n = 152)	Etanercept (n = 349)	Placebo (40 pt. years)	Etanercept (117 pt. years)
Sinusitis	2	3	0.07	0.12

^a Data from 3 trials including a 6-month study in which patients received concurrent methotrexate therapy.

^b Data from 2 of the 3 controlled trials.

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

The following table of suspected adverse reactions is based on clinical trials and/or spontaneous post-marketing reports.

Adverse reaction frequencies are listed below in CIOMS frequency categories:

Very common: $\geq 10\%$

Common: $\geq 1\%$ and $< 10\%$

Uncommon: $\geq 0.1\%$ and $< 1\%$

Rare: $\geq 0.01\%$ and $< 0.1\%$

Very rare: $< 0.01\%$

<i>System</i>	<i>Adverse Reaction</i>
Blood and Lymphatic System Disorders	
Uncommon	Thrombocytopenia, anaemia, leukopenia, neutropenia
Rare	Pancytopenia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
Very Rare	Aplastic anaemia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
Not known	Histocytosis haematophagic (macrophage activation syndrome)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Uncommon	Non-melanoma skin cancers
Rare	Malignant melanoma, lymphoma, leukaemia
Not known	Merkel cell carcinoma
Infections and Infestations	
Very Common	Infections (including upper respiratory tract infections, bronchitis, cystitis, skin infection)*
Common	Serious infections (including pneumonia, cellulitis, arthritis bacterial, sepsis, parasitic infection)*
Rare	Tuberculosis*, opportunistic infections (including invasive fungal, bacterial, protozoal, atypical mycobacterial and viral infections, and <i>Legionella</i> infection)*
Not known	Listeriosis*, hepatitis B reactivation
Immune System Disorders	
Common	Allergic reactions; autoantibody formation
Uncommon	Vasculitis (including ANCA positive vasculitis)
Rare	Serious allergic/anaphylactic reactions (including bronchospasm), sarcoidosis
General Disorders and Administration Site Conditions	

<i>System</i>	<i>Adverse Reaction</i>
Very Common	Injection site reactions (including bleeding, bruising, erythema, itching, pain and swelling)
Common	Pyrexia
Respiratory, Thoracic and Mediastinal Disorders	
Uncommon	Interstitial lung disease (including pulmonary fibrosis and pneumonitis)
Nervous System Disorders	
Rare	Seizures, CNS demyelinating events including multiple sclerosis and localised demyelinating conditions such as optic neuritis and transverse myelitis, peripheral demyelinating events, including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy and multifocal motor neuropathy
Eye Disorders	
Uncommon	Uveitis, scleritis
Skin and Subcutaneous Tissue Disorders	
Common	Pruritus, rash
Uncommon	Angioedema, urticaria, psoriasis (new onset or exacerbation)** and psoriasiform rash
Rare	Cutaneous vasculitis (including leukocytoclastic vasculitis), Stevens-Johnson syndrome, erythema multiforme
Very rare	Toxic epidermal necrolysis
Musculoskeletal, Connective Tissue and Bone Disorders	
Rare	Subacute cutaneous lupus erythematosus, cutaneous lupus erythematosus, lupus-like syndrome
Cardiac Disorders	
Uncommon	Worsening of cardiac failure congestive
Rare	New onset cardiac failure congestive
Hepatobiliary Disorders	
Common	Elevated liver enzymes
Rare	Autoimmune hepatitis

* See additional information, under "Infections" above.

** See additional information under "Psoriasis" above.

Patients with non-radiographic axial spondyloarthritis

The safety observed in adult patients with nr-AxSpA was similar to that seen in previous clinical trials of etanercept in adult patients.

Paediatric patients with juvenile idiopathic arthritis

Brenzys is not indicated for use in children less than 18 years of age. Available data for etanercept treatment in the paediatric population is summarised below:

In general, the adverse events in paediatric patients with juvenile idiopathic arthritis were similar in frequency and type to those seen in adult patients.

JIA patients treated with etanercept had a significantly higher incidence of injection sites reactions (erythema and/or itching, pain or swelling) compared with placebo-treated patients in controlled clinical trials.

Infection was the most common adverse event reported in paediatric patients taking etanercept and occurred at an incidence similar to placebo. The types of infections reported in JIA patients

were generally mild and consistent with those commonly seen in outpatient paediatric populations.

In JIA clinical trials, two cases of varicella infection with signs and symptoms suggestive of aseptic meningitis have been reported among patients treated with etanercept. There were also 4 reports of macrophage activation syndrome.

Long-term safety of etanercept monotherapy (n = 103), etanercept plus methotrexate (n = 294), or methotrexate monotherapy (n = 197) were assessed for up to 3 years in a registry of 594 children aged 2 to 18 years with juvenile idiopathic arthritis, 39 of whom were 2 to 3 years of age. Overall, infections were more commonly reported in patients treated with etanercept compared to methotrexate alone (3.8% versus 2%), and the infections associated with etanercept use were of a more severe nature.

Paediatric patients with plaque psoriasis

Brenzys is not indicated for use in children less than 18 years of age. Available data for etanercept treatment in the paediatric population is summarized below:

In a 48-week study in 211 children aged 4 to 17 years with paediatric plaque psoriasis, the adverse events reported were similar to those seen in previous studies in adults with plaque psoriasis.

Comparative Safety of Brenzys and Enbrel® - Adverse Effects

During clinical studies with Brenzys, 91 healthy subjects were exposed to a single dose of Brenzys, and 299 patients with RA were exposed to Brenzys for up to 52 administrations.

Following the 52 administrations, 126 patients from Brenzys treatment group continued to receive Brenzys (Brenzys/Brenzys) and 119 patients from the Enbrel® treatment group were switched to receive Brenzys (Enbrel®/Brenzys) for up to 48 administrations.

The safety profile of Brenzys was consistent with that previously reported for the etanercept.

During the randomised, double-blind period of Study SB4-G31-RA, 175 (58.5%) patients from the Brenzys treatment group and 179 (60.3%) patients from the Enbrel® treatment group experienced treatment-emergent adverse events (TEAEs). A total of 88 (29.4%) patients from the Brenzys treatment group and 109 (36.7%) patients from the Enbrel® treatment group experienced TEAEs that was determined to be related to the treatment.

During the randomised, double-blind period of Study SB4-G31-RA, the proportions of patients who experience infections and infestations were 85 (28.4%) patients in the Brenzys treatment group vs. 76 (25.6%) patients in the Enbrel® treatment group. Among them, one (0.3%) patient from the Brenzys treatment group and 5 (1.7%) patients from the Enbrel® treatment group were reported to have serious infections and infestations. A total of 11 [3.7%] patients reported to have hepatobiliary adverse events in Study SB4-G31-RA, of which two events in two patients were considered related to Brenzys, and none was reported by patients in the Enbrel® treatment group. Serious hepatobiliary adverse events were reported in 4 [1.3%] patients, all of which were considered unrelated to Brenzys.

Similar proportions of patients reported changes in liver function test (LFT) values following Brenzys or Enbrel® treatment. Alanine aminotransferase (ALT) elevations were reported in 16 [5.4%] patients in the Brenzys treatment group and 10 [3.4%] patients in the Enbrel® treatment group. Aspartate aminotransferase (AST) elevations were reported in 8 [2.7%] patients in Brenzys treatment group and 4 [1.4%] patients in the Enbrel® treatment group.

Up to Week 52, ADAs developed in 3 (1.0%) patients in the Brenzys treatment group and 39 (13.2%) patients in the Enbrel® treatment group. One patient from the Enbrel® treatment group tested positive for neutralising antibody.

Any TEAEs that occurred in $\geq 1\%$ of all patients who received Brenzys or Enbrel® in Study SB4-G31-RA are outlined in Table 4.

Table 4. Percent of RA Patients Reporting Treatment-Emergent Adverse Events $\geq 1\%$ in Controlled Study^a; Full Analysis Set (Study SB4-G31-RA)

System Organ Class	Preferred Term	Brenzys (N = 299)		Enbrel® (N = 297)	
		n	(%)	n	(%)
Blood and Lymphatic System Disorders	Leukopenia	6	2.0	3	1.0
	Anaemia	5	1.7	3	1.0
	Neutropenia	4	1.3	5	1.7
	Thrombocytopenia	3	1.0	0	0.0
	Lymphopenia	2	0.7	4	1.3
	Lymphadenopathy	0	0.0	3	1.0
Ear and Labyrinth Disorders	Vertigo	3	1.0	1	0.3
Gastrointestinal Disorders	Diarrhea	5	1.7	7	2.4
	Abdominal Pain Upper	4	1.3	4	1.3
	Nausea	4	1.3	1	0.3
	Abdominal Pain	2	0.7	3	1.0
	Dyspepsia	2	0.7	4	1.3
	Gastritis	0	0.0	4	1.3
	Vomiting	0	0.0	3	1.0
General Disorders and Administration Site Conditions	Injection Site Erythema	6	2.0	33	11.1
	Influenza Like Illness	3	1.0	1	0.3
	Oedema Peripheral	3	1.0	3	1.0
	Asthenia	2	0.7	5	1.7
	Fatigue	2	0.7	4	1.3
	Injection Site Rash	2	0.7	6	2.0
	Injection Site Reaction	1	0.3	8	2.7
	Injection Site Pruritus	1	0.3	4	1.3
	Application Site Erythema	0	0.0	3	1.0
	Injection Site Oedema	0	0.0	3	1.0
Hepatobiliary Disorders	Cholelithiasis	4	1.3	0	0.0
	Liver Disorder	3	1.0	0	0.0
Infections and Infestations	Upper Respiratory Tract Infection	24	8.0	16	5.4
	Nasopharyngitis	15	5.0	16	5.4
	Viral Infection	7	2.3	5	1.7
	Bronchitis	6	2.0	6	2.0
	Rhinitis	6	2.0	4	1.3
	Pharyngitis	5	1.7	8	2.7
	Urinary Tract Infection	5	1.7	7	2.4
	Oral Herpes	4	1.3	5	1.7
	Herpes Zoster	3	1.0	1	0.3
	Viral Upper Respiratory Tract Infection	2	0.7	3	1.0
Investigations	Alanine aminotransferase increased	18	6.0	17	5.7
	Aspartate Aminotransferase Increased	8	2.7	9	3.0
	Gamma-Glutamyltransferase Increased	5	1.7	5	1.7
	Lymphocyte Count Decreased	4	1.3	6	2.0

System Organ Class	Preferred Term	Brenzys (N = 299)		Enbrel® (N = 297)	
		n	(%)	n	(%)
	Transaminases Increased	4	1.3	4	1.3
	Blood Pressure Increased	3	1.0	3	1.0
	Liver Function Test Abnormal	3	1.0	2	0.7
Musculoskeletal and Connective Tissue Disorders	Rheumatoid Arthritis	9	3.0	10	3.4
	Arthralgia	4	1.3	5	1.7
	Back Pain	4	1.3	4	1.3
Nervous System Disorder	Headache	13	4.3	8	2.7
	Dizziness	2	0.7	7	2.4
Respiratory, Thoracic and Mediastinal Disorders	Oropharyngeal Pain	4	1.3	1	0.3
	Cough	4	1.3	10	3.4
Skin and Subcutaneous Tissue Disorders	Rash	6	2.0	4	1.3
	Dry Skin	3	1.0	1	0.3
	Rash Papular	3	1.0	1	0.3
	Alopecia	2	0.7	3	1.0
	Erythema	2	0.7	10	3.4
	Hyperhidrosis	2	0.7	3	1.0
	Pruritus	2	0.7	4	1.3
Vascular Disorders	Hypertension	11	3.7	11	3.7

^a Includes data from randomised, double-blind period (up to Week 52).

N = Number of patients having received at least 1 dose of Brenzys or Enbrel®.

% = n/N*100

Full Analysis Set (FAS) = FAS consisted of all patients who were randomised at the Randomisation Visit. Following the intent-to-treat principle, patients were analysed according to the treatment they were assigned at randomisation. However, patients who did not qualify for randomisation and were inadvertently randomised into the study were excluded from the FAS, provided these patients did not receive any Brenzys or Enbrel® during that study phase.

The safety profiles during the open-label, extension period (after Week 52 up to Week 100) were also comparable between the treatment groups. A total of 60 (47.6%) patients from the Brenzys/Brenzys treatment group and 58 (48.7%) patients from the Enbrel®/Brenzys treatment group were newly reported to have TEAEs. In 17 (13.5%) patients of the Brenzys/Brenzys treatment group and 16 (13.4%) patients of the Enbrel®/Brenzys treatment group, these newly reported TEAEs were considered to be related to the treatment. No new cases of injection site reactions were reported in either treatment group.

Any TEAEs that occurred in ≥ 2% of all patients who received Brenzys or Enbrel® in Study SB4-G31-RA are outlined in Table 5.

Table 5. Percent of RA Patients Reporting Treatment-Emergent Adverse Events ≥ 2% in Controlled Study in Open-label, Extension Period; Extended Population (Study SB4-G31-RA)

System Organ Class	Preferred Term	Brenzys/Brenzys (N = 126)		Enbrel®/Brenzys (N = 119)	
		n	(%)	n	(%)
Gastrointestinal Disorders	Dyspepsia	0	0.0	3	2.5
Infections and Infestations	Upper Respiratory Tract Infection	10	7.9	9	7.6
	Pharyngitis	9	7.1	5	4.2
	Bronchitis	6	4.8	7	5.9
	Nasopharyngitis	6	4.8	5	4.2
	Laryngitis	4	3.2	0	0.0
	Viral Infection	4	3.2	1	0.8
	Respiratory Tract Infection	3	2.4	1	0.8

Musculoskeletal and Connective Tissue Disorder	Rheumatoid Arthritis	7	5.6	3	2.5
	Arthralgia	3	2.4	2	1.7
Vascular Disorders	Hypertension	1	0.8	5	4.2

Extended Population = Extended population consisted of all enrolled patients who had completed Week 52 treatment of the randomised, double-blind period, and who had received at least one dose of Brenzys in the open-label extension period.

N = number of patients in the Extended population; n = number of patients with TEAEs which were related with Brenzys.

Percentages were based on N.

Two (1.7%) cases of oral candidiasis and 2 (1.7%) cases of cardiac failure were reported for patients who switched from Enbrel® to Brenzys treatment.

ADAs developed in one patient from the Brenzys/Brenzys treatment group and in one patient from the Enbrel®/Brenzys treatment group. All the ADA positive samples were non-neutralising and low titre. The long term safety and immunogenicity profiles of Brenzys during the open-label extension period were consistent with the profiles observed during the randomised, double-blind period.

4.9 OVERDOSE

The maximum tolerated dose of etanercept has not been established in humans. Repeat-dose studies have been performed in cynomolgus monkeys at doses resulting in AUC-based systemic exposure levels of etanercept that were over 13-fold higher than in humans at the highest proposed therapeutic dose of 50 mg and have revealed no dose-limiting or target organ toxicity. No dose-limiting toxicities were observed during clinical trials of RA patients. The highest dose level evaluated has been an IV loading dose of 32 mg/m² followed by SC doses of 16 mg/m² administered twice weekly. One RA patient mistakenly self-administered 62 mg etanercept SC twice weekly for three weeks without experiencing unexpected side effects. Single IV doses up to 60 mg/m² (approximately twice the recommended dose) have been administered to healthy volunteers in an endotoxaemia study without evidence of dose-limiting toxicities.

There is no known antidote to etanercept.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Pro-inflammatory molecules that are linked in a network controlled by TNF mediate much of the joint pathology in rheumatoid arthritis (RA) and ankylosing spondylitis (AS) and skin pathology in plaque psoriasis. The mechanism of action of etanercept is thought to be its competitive inhibition of TNF binding to cell surface TNFR, preventing TNF-mediated cellular responses by rendering TNF biologically inactive. Etanercept may also modulate biological responses controlled by additional downstream molecules (e.g., cytokines, adhesion molecules, or proteinases) that are induced or regulated by TNF.

Pharmacodynamics

Etanercept binds specifically to tumour necrosis factor (TNF) and blocks its interaction with cell surface TNF receptors. Etanercept did not induce complement-mediated cytolysis of murine T cells that expressed TNF on the cell surface. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. TNF is a dominant cytokine in the inflammatory process of rheumatoid arthritis. Elevated levels of TNF are also found in the synovium and psoriatic plaques of patients with psoriatic arthritis and in serum and synovial tissue of patients with ankylosing spondylitis. In plaque psoriasis, infiltration by inflammatory cells including T-cells leads to increased TNF levels in psoriatic lesions, compared with levels in uninvolved skin.

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. It inhibits the activity of TNF *in vitro* and has been shown to affect several animal models of inflammation, including murine collagen-induced arthritis. Etanercept inhibits binding of both TNF α and TNF β (lymphotoxin alpha [LT α]) to cell surface TNFRs, rendering TNF biologically inactive. Cells expressing transmembrane TNF that bind etanercept are not lysed *in vitro* in the presence or absence of complement.

Comparability of Brenzys with Enbrel® - Pharmacodynamic Properties

Comparability assessment of pharmacodynamic *in vitro* studies including binding and cell based assays, as well as an *in vivo* efficacy study in BALB/c mice support similar/equivalent pharmacological activity of Brenzys compared to Enbrel®.

The *in vitro* assays were closely associated with the mode of action of etanercept (including TNF- α , LT- α 3 binding assays and the NF- κ B reporter gene assay). In addition, Fc-related binding and functional activities were assessed, although the main function of the Fc-region of etanercept is to prolong half-life rather than to impart on Fc-mediated effector activity. Similarity between the activities of Brenzys and Enbrel® were demonstrated in these *in vitro* studies.

An *in vivo* study was conducted to demonstrate similar suppressive activity of Brenzys and Enbrel® on TNF- α mediated pathology in a mouse (BALB/c) model of collagen antibody-induced arthritis. Both products suppressed the development of arthritis, as determined by changes in footpad volumes and clinical scores, with no significant differences among treated groups.

Clinical trials with Enbrel®

This section presents data from 5 randomised controlled studies with etanercept in adults with rheumatoid arthritis, 2 studies in adults with ankylosing spondylitis, 1 study in adults with non-radiographic axial spondyloarthritis, 1 study in adults with psoriatic arthritis, 2 studies in adults with plaque psoriasis.

Adult rheumatoid arthritis

Placebo-controlled studies

The efficacy of etanercept was assessed in a randomised, double-blind, placebo-controlled study. The study evaluated 234 adult patients with active rheumatoid arthritis who had failed therapy with at least one but no more than four disease-modifying antirheumatic drugs (DMARDs). Doses of 10 mg or 25 mg etanercept or placebo were administered subcutaneously twice a week for 6 consecutive months. The results of this controlled trial were expressed in percentage improvement in rheumatoid arthritis using American College of Rheumatology (ACR) response criteria. The primary endpoint was achievement of an ACR20 response at month 3. Subjects who failed to respond based on pre-specified criteria for lack of efficacy

before month 3 were allowed to drop out early and were considered treatment failures. ACR20 and 50 responses were higher in patients treated with etanercept at 3 and 6 months than in patients treated with placebo, at all-time points as seen in the table below.

Table 6. ACR Responses (% of Patients)

Response	Placebo (n=80)	Etanercept ^a (n=78)
ACR20		
Month 3	23	62 ^b
Month 6	11	59 ^b
ACR50		
Month 3	8	41 ^b
Month 6	5	40 ^b

^a 25 mg etanercept SC twice weekly.

^b $p \leq 0.01$, Etanercept vs. placebo.

Approximately 15% of subjects who received etanercept achieved an ACR70 response at month 3 and month 6 compared to fewer than 5% of subjects in the placebo arm. Among patients receiving etanercept, the clinical responses generally appeared within 1 to 2 weeks after initiation of therapy and nearly always occurred by 3 months. A dose response was seen; results with 10 mg were intermediate between placebo and 25 mg. Etanercept was significantly better than placebo in all components of the ACR criteria as well as other measures of rheumatoid arthritis disease activity not included in the ACR response criteria, such as morning stiffness. A Health Assessment Questionnaire (HAQ), which included disability, vitality, mental health, general health status and arthritis-associated health status sub-domains, was administered every 3 months during the trial. All sub-domains of the HAQ were improved in patients treated with etanercept compared to controls at 3 and 6 months.

After discontinuation of etanercept, symptoms of arthritis generally returned within a month. Reintroduction of treatment with etanercept after discontinuations of up to 24 months resulted in the same magnitudes of response as patients who received etanercept without interruption of therapy based on results of open-label studies. Continued durable responses have been seen in open-label extension treatment trials when patients received etanercept without interruption.

A second randomised, double-blind, placebo-controlled study also compared the safety and efficacy of etanercept (25 mg) against placebo (SC, twice a week over 6 months) in 89 RA patients in addition to a stable dose of methotrexate. The ACR response criteria were used to assess efficacy. The primary endpoint was achievement of an ACR20 response at 6 months. Responses were higher in patients treated with etanercept at 3 and 6 months. Clinical responses in etanercept-treated patients generally appeared after 1-2 weeks of therapy. In addition, approximately 15% of etanercept-treated patients achieved an ACR70 response at month 3 and month 6, compared to less than 5% of subjects in the placebo arm. Etanercept-treated patients experienced significantly greater improvements in all components of the ACR criteria, compared to patients in the placebo arm.

The safety and efficacy of 50 mg etanercept (two 25 mg SC injections) administered once weekly were evaluated in a double-blind, placebo-controlled study of 420 patients with active RA. In this study, 53 patients received placebo, 214 patients received 50 mg etanercept once weekly and 153 patients received 25 mg etanercept twice weekly. The safety and efficacy profiles of the two etanercept treatment regimens were comparable in their effect on signs and symptoms of RA.

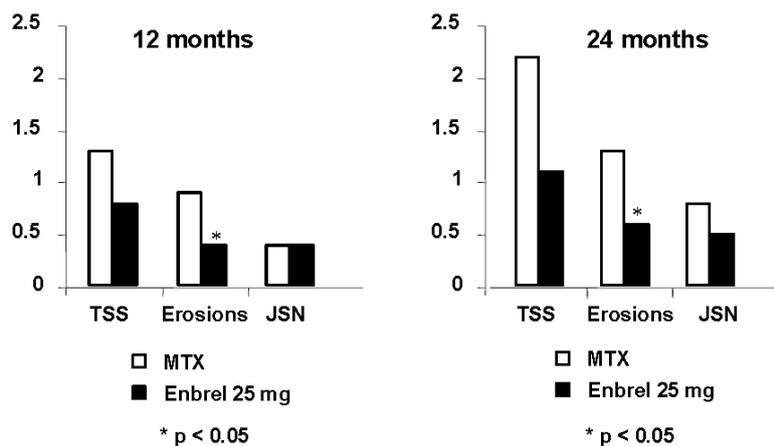
Active-controlled studies

A randomised, active-controlled study with blinded radiographic evaluations as a primary endpoint compared the efficacy of etanercept to oral methotrexate in 632 adult patients with

active rheumatoid arthritis (< 3 years duration) who had never received treatment with methotrexate. The patients had to have >12 tender joints, > 10 swollen joints and either ESR > 28 mm/hr, CRP > 2.0 mg/dL, or morning stiffness for > 45 minutes. Patients were at high risk of erosive disease defined as being rheumatoid factor positive or having at least three erosions at baseline. Doses of 10 mg or 25 mg etanercept were administered SC twice a week for up to 24 months. Methotrexate doses were escalated from 7.5 mg/week to a maximum of 20 mg/week over the first 8 weeks of the trial and continued for up to 24 months. Clinical improvement including onset of action within 2 weeks with etanercept 25 mg was similar to that seen in the previous 2 trials and was maintained for up to 24 months. At baseline, patients had a moderate degree of disability, with mean HAQ scores of 1.4 to 1.5. Treatment with etanercept 25 mg resulted in substantial improvement at 12 months, with about 44% of patients achieving a normal HAQ score (less than 0.5). This benefit was maintained in Year 2 of this study.

In this study, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and joint space narrowing score (JSN). Radiographs of hands/wrists and feet were read at baseline and 6, 12 and 24 months. The 10 mg etanercept dose had consistently less effect on structural damage than the 25 mg dose. Etanercept 25 mg was significantly superior to methotrexate for erosion scores at both 12 and 24 months. The differences in TSS and JSN were not statistically significant between methotrexate and etanercept 25 mg. The results are shown in Figure 1.

Figure 1. Radiographic Progression over 24 Months



In another active-controlled, double-blind, randomised study, clinical efficacy, safety and radiographic progression in RA patients treated with etanercept alone (25 mg twice weekly), methotrexate alone (7.5 to 20 mg weekly, median dose 20 mg) and of the combination of etanercept and methotrexate initiated concurrently were compared in 682 adult patients with active rheumatoid arthritis of 6 months to 20 years duration (median 5 years) who had a less than satisfactory response to at least 1 DMARD other than methotrexate. Forty-three percent of patients had previously received methotrexate a mean of 2 years prior to the trial at a mean dose of 12.9 mg/week. Patients were excluded from this study if methotrexate had been discontinued for lack of efficacy or for safety considerations.

Patients in the etanercept in combination with methotrexate therapy group had significantly higher ACR20, ACR50, ACR70 responses and improvement for disease activity scores (DAS) at both 24 and 52 weeks than patients in either of the single therapy groups (results shown in Table 7).

Table 7. Clinical Efficacy Results: Comparison of Etanercept vs. Methotrexate vs. Etanercept in Combination with Methotrexate in Patients with RA of 6 Months to 20 Years Duration

Endpoint Time Point	Methotrexate (n = 228)	Etanercept (n = 223)	Etanercept + Methotrexate (n = 231)
ACR20 Response			
Week 24	73.7%	71.3%	81.8% †,ϕ
Week 52	75.0%	75.8%	84.8% †,ϕ
ACR50 Response			
Week 24	40.8%	40.4%	59.3% †,ϕ
Week 52	42.5%	48.4%	69.3% †,ϕ
ACR70 Response			
Week 24	15.4%	17.0%	35.9% †,ϕ
Week 52	18.9%	24.2%	42.9% †,ϕ
DAS ^a			
Baseline score	5.5	5.7	5.5
Week 24 score	3.1	3.1	2.5 †,ϕ
Week 52 score	3.0	3.0	2.3 †,ϕ

^a Values for DAS are means.

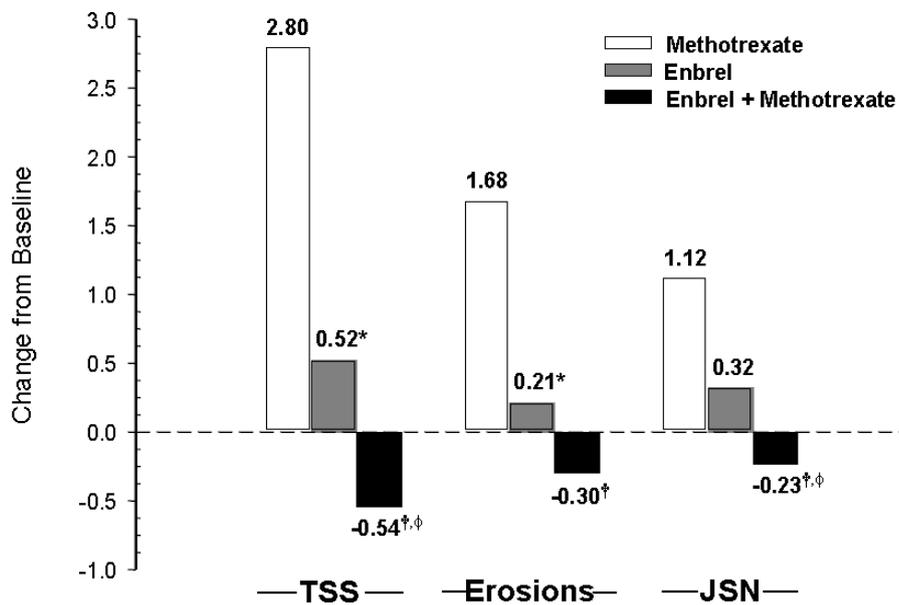
Pairwise comparison p-values: † = p < 0.05 for comparisons of etanercept + methotrexate vs. methotrexate and ϕ = p < 0.05 for comparisons of etanercept + methotrexate vs. etanercept

The percentage of patients who achieved low disease activity (defined as DAS < 2.4) at 52 weeks was 39%, 35% and 61% for patients in the etanercept alone group, methotrexate alone group and the etanercept combination group, respectively. Remission (defined as DAS < 1.6) was experienced by 18%, 14% and 37% of patients administered etanercept alone, methotrexate alone and combination therapy respectively.

Mean HAQ scores improved from baseline levels of (1.7, 1.7 and 1.8) to (1.0, 1.1 and 0.8) at 52 weeks in the etanercept, methotrexate and etanercept in combination with methotrexate treatment groups, respectively (combination versus both methotrexate and etanercept, p < 0.01).

Radiographic progression as measured by Total Sharp Score (TSS) was significantly less in the etanercept group than in the methotrexate group at week 52. Significantly less radiographic progression (TSS) was observed with etanercept in combination with methotrexate compared with etanercept alone or methotrexate alone at week 52. The results for radiographic results (TSS), joint erosion and joint space narrowing (JSN) at week 52 are shown in Figure 2. There was a significant decrease in TSS compared with baseline in the combination of etanercept with methotrexate group.

Figure 2. Radiographic Progression: Comparison of Etanercept vs. Methotrexate vs. Etanercept in Combination with Methotrexate in Patients with RA of 6 Months to 20 Years Duration (52-Week Results)



Pairwise comparison p-values: * = $p < 0.05$ for comparisons of etanercept vs. methotrexate, † = $p < 0.05$ for comparisons of etanercept + methotrexate vs. methotrexate and ϕ = $p < 0.05$ for comparisons of etanercept + methotrexate vs. etanercept

The percentage of patients without progression (TSS change ≤ 0.5) was higher in the etanercept in combination with methotrexate and etanercept groups compared with methotrexate at week 24 (74%, 68% and 56%, respectively; $p < 0.05$) and week 52 (80%, 68% and 57%, respectively; $p < 0.05$).

Safety, efficacy and immunogenicity were assessed in an open label study of etanercept manufactured by the serum-free process (SFP) in patients with rheumatoid arthritis. Based on indirect comparisons with historical data, the results were comparable to two previous phase 3 controlled studies in subjects with RA using etanercept manufactured by a serum-based process.

Adults with psoriatic arthritis

The efficacy of etanercept was assessed in a randomised, double-blind, placebo-controlled study of 205 patients with psoriatic arthritis. Patients were between 18 and 70 years of age and had active psoriatic arthritis (≥ 3 swollen joints and ≥ 3 tender joints) in at least one of the following forms: (1) distal interphalangeal (DIP) involvement; (2) polyarticular arthritis (absence of rheumatoid nodules and presence of psoriasis); (3) arthritis mutilans; (4) asymmetric psoriatic arthritis; or (5) spondylitis-like ankylosis. Patients also had plaque psoriasis with a qualifying target lesion ≥ 2 cm in diameter. Patients currently on methotrexate therapy (stable for ≥ 2 months) could continue at a stable dose of 25 mg/week methotrexate. Doses of ≤ 25 mg etanercept or placebo were administered SC twice a week for 6 months. At the end of the double-blind study, patients could enter a long-term open-label extension study for a total duration of up to 2 years.

The clinical responses were expressed as percentages of patients achieving the ACR 20, 50 and 70 response and percentages with improvement in Psoriatic Arthritis Response Criteria (PsARC). The PsARC endpoint comprises of four measures: (1) patient global assessment, (2)

physician global assessment, (3) joint pain/tenderness score and (4) joint swelling score. Achievement of the PsARC endpoint requires improvement in at least two of the four measures, one of which must be joint pain/tenderness or swelling and no worsening in any of the four measures. Data have not been evaluated to establish whether etanercept inhibits progressive joint destruction in psoriatic arthritis. Results are summarised in the table below.

Table 8. ACR and PsARC Responses of Patients with Psoriatic Arthritis in Placebo-Controlled Trial

Endpoint Time Point	Percent of Patients Placebo (n = 104)	Etanercept (n = 101)
ACR20		
Month 3	15	59 ^b
Month 6	13	50 ^b
ACR50		
Month 3	4	38 ^b
Month 6	4	37 ^b
ACR70		
Month 3	0	11 ^b
Month 6	1	9 ^c
PsARC		
Month 3	31	72 ^b
Month 6	23	70 ^b

In this study, the psoriatic skin lesions of patients with active arthritis were also improved with etanercept treatment compared with placebo. In a subset of patients with psoriasis involvement $\geq 3\%$ of body surface area, improvements in the Psoriasis Area and Severity Index (PASI) were assessed at Month 3 and Month 6. The PASI is a composite score calculated from disease activity scores and the fraction of body surface area involvement. PASI results are presented in Table 9.

Table 9. PASI Responses of Patients with Psoriatic Arthritis in Placebo-Controlled Trial

Endpoint Time Point	Percent of Patients Placebo (n = 62)	Etanercept^a (n = 66)
PASI 50% improvement		
Month 3	15	36 ^c
Month 6	18	47 ^b
PASI 75% improvement		
Month 3	8	12
Month 6	3	23 ^c

^a 25 mg etanercept SC twice weekly

^b $p < 0.001$, etanercept vs. placebo

^c $p < 0.01$, etanercept vs. placebo

Among patients with psoriatic arthritis who received etanercept, the clinical responses were apparent at the time of the first visit (4 weeks) and were maintained through 6 months of therapy. etanercept was significantly better than placebo in all measures of disease activity ($p < 0.001$) and responses were similar with and without concomitant methotrexate therapy.

In this study, structural joint damage was assessed radiographically and expressed as change in modified Total Sharp Score (TSS) and its components, the erosion score and joint space narrowing score (JSN). The possible range for the modified TSS was 0 to 370. Radiographs of hands and wrists were obtained at baseline and months 6, 12 and 24.

The 1-year analyses, as shown in the table below, indicates that the difference between treatment groups was significant for mean annualized rate of change from baseline in TSS, erosion scores and for JSN. In addition, significantly more subjects in the etanercept group had no progression (≤ 0 change) in TSS from baseline, compared with subjects in the placebo group.

Table 10. Annualised Rate of Change (Mean + SE) at 1 Year

	Placebo (n = 104) ^a	Etanercept (n = 101) ^a	p-Value
TSS	1.00 (0.29)	-0.03 (0.09)	0.0001 ^b
Erosions	0.66 (0.17)	-0.09 (0.07)	0.0001 ^b
JSN	0.34 (0.13)	0.05 (0.05)	0.0438 ^b
Number (%) of subjects with ≤ 0 change in TSS	63 (61) ^d	81 (80)	0.0027 ^c

Abbreviations: JSN = joint space narrowing; SE = standard error; TSS = total Sharp score.

^a Number of randomized and treatment subjects.

^b p-Values were determined using the van Elteren test with stratification for methotrexate use and reader pair (in the case of TSS, p was significant in the methotrexate and no methotrexate strata).

^c p-Value was determined using the Cochran-Mantel-Haenszel test with stratification for methotrexate use and reader pair.

^d The high placebo effect was attributed to the taking of etanercept by some patients in the overlap period following 6 months on placebo in the double-blind period.

The modified TSS at 6, 12 and 24 months are presented in the following table for those patients who entered year 2 and provided radiographs during the second year of the study.

Table 11. Radiographic Progression (Mean + Standard Error Change) Annualized Change from Baseline in Total Sharp Score, Erosion and Joint Space Narrowing Scores over Time, Month 6 to Year 2^a

	Placebo/Etanercept (n = 70) ^b	Etanercept (n = 71) ^b
Mean (SE) change in TSS		
6 months	0.39 (0.13)	-0.33 (0.10)
1 year	0.72 (0.27)	-0.28 (0.15)
2 years	0.50 (0.24)	-0.38 (0.25)
Mean (SE) change in erosions		
6 months	0.27 (0.11)	-0.29 (0.09)
1 year	0.48 (0.20)	-0.31 (0.14)
2 years	0.23 (0.17)	-0.40 (0.18)
Mean (SE) change in JSN		
6 months	0.12 (0.06)	-0.04 (0.05)
1 year	0.24 (0.11)	0.03 (0.07)
2 years	0.27 (0.11)	0.02 (0.11)

Abbreviations: JSN = joint space narrowing; SE = standard error; TSS = total Sharp score.

^a Patients in this study were originally randomized to etanercept or to placebo. The study design included a blinded maintenance period that continued until all patients had completed at least 6 months of treatment. After the last patient completed 6 months of treatment, an open-label phase followed in which all patients received etanercept.

^b Number of randomized and treated subjects with radiograph at year 2 time point.

In subjects who received placebo during the controlled part of the study and etanercept in the open-label part, further radiographic progression was inhibited after subjects began receiving etanercept. Etanercept treatment resulted in improvement in physical function during the double-blind period and this benefit was maintained during the longer-term exposure of up to 2 years.

Quality of life in psoriatic arthritis patients was assessed using the Health Assessment Questionnaire (HAQ) and SF-36 instruments. There was a statistically significant improvement

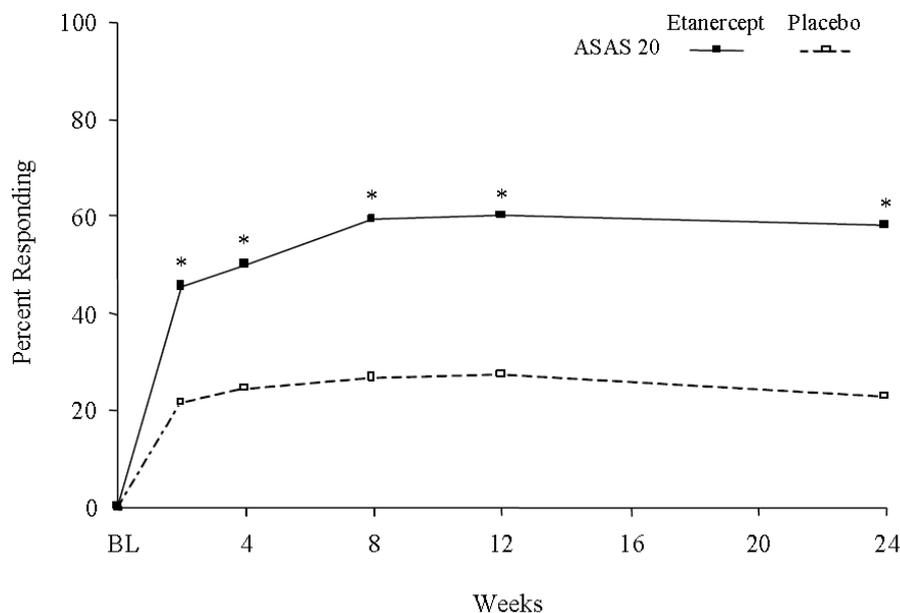
in mean HAQ score from 1.1 to 0.5 on a scale of 0 to 3 for patients treated with etanercept. The SF-36 showed improvements in the physical but not the mental components of the quality of life score.

Adults with ankylosing spondylitis

The efficacy of etanercept was assessed in 2 randomised, double-blind, placebo-controlled studies in 361 patients with ankylosing spondylitis. The largest of these trials (n = 277) enrolled patients who were between 18 and 70 years of age and had active ankylosing spondylitis as defined by the modified New York Criteria for Ankylosing Spondylitis. Patients were to have evidence of active disease based on visual analog scale (VAS) scores of ≥ 30 for average of duration and intensity of morning stiffness plus VAS scores of ≥ 30 for at least 2 of the following 3 parameters: patient global assessment; average of VAS values for nocturnal back pain and total back pain; average of 10 questions on the Bath Ankylosing Spondylitis Functional Index (BASFI). The duration of this study was up to 24 weeks and patients had a mean diagnosis of AS for 10 years. Patients with complete ankylosis of the spine were excluded from study participation. Patients taking hydroxychloroquine, sulfasalazine, methotrexate or prednisolone (≤ 10 mg/day) or equivalent, could continue these drugs at stable doses for the duration of the study. Doses of 25 mg of etanercept (based on dose-finding studies in patients with rheumatoid arthritis) or placebo were administered subcutaneously twice a week for 6 months.

The primary measure of efficacy was a 20% improvement in the Assessment in Ankylosing Spondylitis (ASAS 20) response criteria. Compared to placebo, treatment with etanercept resulted in significant improvements in clinical response as early as 2 weeks after the initiation of therapy (see figure below).

Figure 3. ASAS 20 Response in Patients with Ankylosing Spondylitis in a Placebo-Controlled Trial



*p < 0.001 for etanercept vs. placebo.

At 12 weeks, the ASAS 20/50/70 responses were achieved by 60%, 45% and 29%, respectively, of patients receiving etanercept, compared to 27%, 13% and 7%, respectively, of patients receiving placebo (p < 0.001 for etanercept vs placebo). Similar results were seen at week 24.

Table 12. Components of Ankylosing Spondylitis Disease Activity

	Placebo n = 139		Etanercept ^a n = 138	
	baseline	6 months	baseline	6 months
ASAS response criteria				
Patient global assessment ^b	63	56	63	36
Back pain ^c	62	56	60	34
BASFI ^d	56	55	52	36
Inflammation ^e	64	57	61	33
Acute phase reactants				
CRP (mg/dL) ^f	2.0	1.9	1.9	0.6
Spinal mobility (cm):				
Modified Schober's test	3.0	2.9	3.1	3.3
Chest expansion	3.2	3.0	3.3	3.9
Occiput-to-wall measurement	5.3	6.0	5.6	4.5

^a p < 0.0015 for all comparisons between etanercept and placebo at 6 months. p-values for continuous endpoints were based on percent change from baseline.

^b Measured on a Visual Analog Scale (VAS) scale with 0 = "none" and 100 = "severe."

^c Average of total nocturnal and back pain scores, measured on a VAS scale with 0 = "no pain" and 100 = "most severe pain."

^d Bath Ankylosing Spondylitis Functional Index (BASFI), average of 10 questions.

^e Inflammation represented by the average of the last 2 questions on the 6-question Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).

^f C-reactive protein (CRP) normal range: 0 - 1.0 mg/dL.

Adults with non-radiographic axial spondyloarthritis

The efficacy of etanercept in patients with non-radiographic axial spondyloarthritis (nr-AxSpA) was assessed in a randomised, 12-week double-blind, placebo-controlled study followed by an open-label period for up to an additional 92 weeks. The study evaluated 215 adult patients (modified intent-to-treat population) with active (baseline BASDAI score of ≥ 4) nr-AxSpA (18 to 49 years of age), defined as those patients meeting the ASAS classification criteria of axial spondyloarthritis but not the modified New York criteria for AS. Patients were also required to have an inadequate response or intolerance to two or more NSAIDs. In the double-blind period, patients received etanercept 50 mg weekly or placebo for 12 weeks and in the open-label period, all patients received etanercept 50 mg weekly for up to an additional 92 weeks. Throughout the study, patients were required to continue on an optimal tolerated dose of NSAIDs. The primary measure of efficacy was a 40% improvement in at least three of the four ASAS domains and absence of deterioration (ASAS 40) in the remaining domain at week 12 of the double-blind period. MRIs of the sacroiliac joint and spine and CRP were obtained to assess inflammation at baseline and at week 12. Results from the double-blind period are included below, unless noted otherwise.

Compared to placebo, treatment with etanercept resulted in statistically significant improvement in the ASAS 40, ASAS 20 and ASAS 5/6. Significant improvement was also observed for the ASAS partial remission and BASDAI 50. Week 12 results are shown in the following table.

Table 13. Efficacy Response in Placebo-Controlled nr-AxSpA Study: Percent of Patients Achieving Clinical Endpoints

Double-Blind Clinical Responses at Week 12	Placebo N=106 to 109*	Etanercept N=103 to 105*
Primary Endpoint		
ASAS** 40	15.7 [†]	32.4 ^{a †}
Secondary Endpoint		
ASAS 20	36.1	52.4
ASAS 5/6	10.4	33.0

ASAS partial remission	11.9	24.8
BASDAI*** 50	23.9	43.8

† Difference in proportions % (95% CI) = 16.64 (5.36, 27.92)

* Some patients did not provide complete data for each endpoint

** ASAS=Assessments in Spondyloarthritis International Society

*** Bath Ankylosing Spondylitis Disease Activity Index

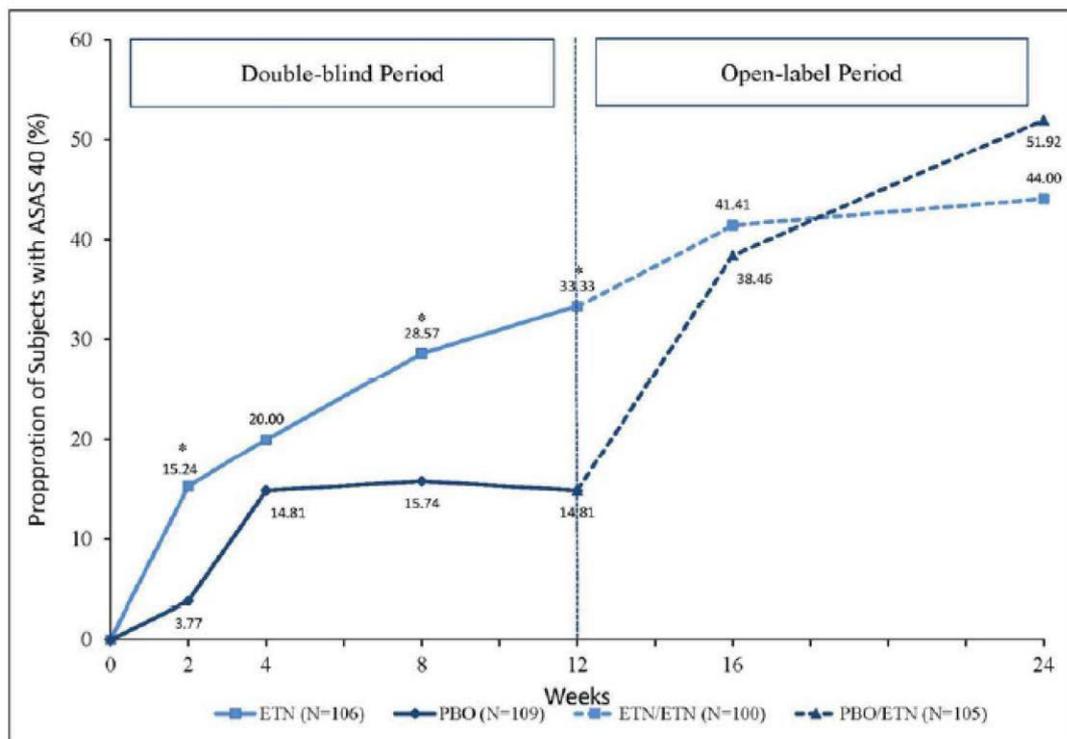
^a p < 0.01 between etanercept and placebo

At week 12, there was an improvement in the secondary MRI endpoint SPARCC (Spondyloarthritis Research Consortium of Canada) score for the sacroiliac joint for patients receiving etanercept. Adjusted mean change from baseline was -3.8 for etanercept treated (n = 95) versus -0.8 for placebo treated (n = 105) patients .

The secondary endpoints physical function and health-related quality of life were assessed using the BASFI (Bath Ankylosing Spondylitis Functional Index), EuroQol 5D and the SF-36 questionnaires. etanercept showed greater improvement in the BASFI, EQ5D Overall Health State Score and the SF-36 Physical Component Score (PCS) from baseline to week 12 compared to placebo. Other measures of quality of life and anxiety/depression scales (including Ankylosing Spondylitis Quality of Life (ASQoL) Scores, Ankylosing Spondylitis Work Instability Index (AS-WIS) and Hospital Anxiety and Depression Scale (HADS)), and the Bath Ankylosing Spondylitis Patient Global Assessment Score (BAS-G), all secondary endpoints, showed no evidence of difference between the etanercept and placebo groups.

Clinical responses among nr-AxSpA patients who received etanercept (as assessed by ASAS 40) were apparent at the time of the first visit (2 weeks) and were maintained through 2 years of therapy. Improvements in health-related quality of life (as assessed by SF-36) and physical function (as assessed by BASFI) were also maintained through 2 years of therapy.

Figure 4. Efficacy Response In Placebo-Controlled nr-AxSpA Study: Proportion of Patients Achieving ASAS 40, mITT Population (Double-blind and Open-label Periods)



* $p < 0.05$ (Double-blind period only)

ETN = etanercept 50 mg weekly, mITT = modified intent-to-treat, N = number of subjects randomised, PBO = placebo.

The proportions of subjects in the mITT who achieved ASAS 40 were measured at a number of time points in the open label period. At Week 12, 101 subjects who had been randomised to etanercept contributed to the ASAS 40 outcome. By Week 104, 81 subjects who had been randomised to etanercept contributed to the ASAS 40 outcome. Last observation carried forward was used to handle missing values. Based on exploratory analyses, there were no decreases in the proportions of subjects who achieved ASAS 40 at the measurement time points over the open label period compared to Week 12. There are no data on the effects of etanercept on disease progression or structural damage in nr-AxSpA patients. The 2 year data did not reveal any new safety findings.

Adults with plaque psoriasis

The safety and efficacy of etanercept were assessed in two randomised, double-blind, placebo-controlled studies. Study 1 evaluated 652 patients with chronic plaque psoriasis who were ≥ 18 years old, had active but clinically stable plaque psoriasis involving $\geq 10\%$ of the body surface area and had a minimum psoriasis area and severity index (PASI) of 10 at screening. etanercept was administered subcutaneously at doses of 25 mg once a week, 25 mg twice a week or 50 mg twice a week for 6 consecutive months. During the first 12 weeks of the double-blind treatment period, patients received placebo or one of the above three etanercept doses. After 12 weeks of treatment, patients in the placebo group began treatment with blinded etanercept (25 mg twice weekly); patients in the active treatment groups continued to week 24 on the dose to which they were originally randomised. This study also had a drug withdrawal period during which patients who achieved PASI improvement of at least 50% at week 24 had treatment stopped. Patients were observed off treatment for the occurrence of rebound (PASI $\geq 150\%$ of baseline) and for the time to relapse (defined as a loss of at least half of the improvement achieved between baseline and week 24). Upon relapse, patients were retreated with etanercept in a blinded fashion at the dose they had been receiving at week 24.

Study 2 evaluated 583 patients and had the same inclusion criteria as study 1. Patients in this study received a dose of 25 mg or 50 mg etanercept, or placebo subcutaneously twice a week for 12 weeks and then all patients received open-label 25 mg etanercept twice weekly for an additional 24 weeks.

The primary efficacy endpoint in both studies was the proportion of patients in each treatment group that achieved the PASI 75 (i.e., at least a 75% improvement in the PASI score from baseline) at 12 weeks. The results of the primary and secondary endpoints of both studies are shown below.

Table 14. Responses of Patients with Psoriasis in Studies 1 and 2

Response	Study 1					Study 2		
	Placebo n=166 wk 12	Etanercept				Placebo n=193 wk 12	Etanercept	
		25 mg BIW n=162 wk 12	25 mg BIW n=162 wk 24 ^a	50 mg BIW n=164 wk 12	50 mg BIW n=164 wk 24 ^a		25 mg BIW n=196 wk 12	50 mg BIW n=196 wk 12
PASI 50, %	14	58*	70	74*	77	9	64*	77*
PASI 75, %	4	34*	44	49*	59	3	34*	49*
PASI 90, %	1	12*	20	22*	30	1	11*	21*
Dermatologist static global assessment, clear or almost clear, % (0 or 1 on 0-5 scale)	5	34*	39	49*	55	4	39*	57*
Percent improvement from baseline in PASI, mean	14.0	52.6*	62.1	64.2*	71.1	0.2	56.8*	67.5*
Patient global assessment of psoriasis, median (0-5 scale)	4.0	2.0*	2.0	1.5*	1.0	4.0	2.0*	1.0*
Percent improvement from baseline in Dermatology Life Quality Index, mean	10.9	50.8*	59.4	61.0*	73.8	6.2	65.4*	70.2

*p ≤ 0.0001 compared with placebo

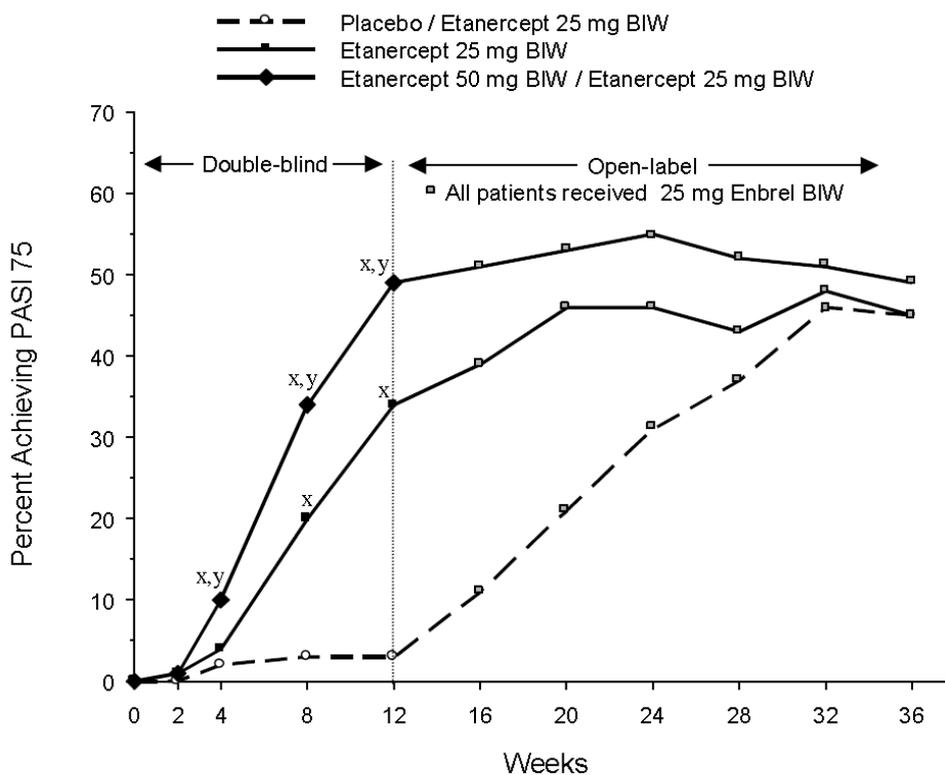
^aNo statistical comparisons to placebo were made at week 24 in Study 1 because the original placebo group began receiving etanercept 25 mg BIW from week 13 to week 24.

Among patients with plaque psoriasis who received etanercept, significant responses relative to placebo were apparent at the time of the first visit (2 weeks) for the mean percent improvement in PASI, Dermatologist Static Global Assessment of Psoriasis, Dermatology Life Quality Index and Patient Global Assessment of Psoriasis and were maintained through 24 weeks of therapy.

During the withdrawal period in study 1, symptoms of psoriasis gradually returned with a median time to disease relapse of 3 months. No rebound flare of disease and no psoriasis-related adverse events were observed. Retreatment with etanercept resulted in a similar magnitude of response as was seen during the initial double-blind portion of the study.

At weeks 4, 8 and 12 of study 2, the 50 mg twice weekly group had a significantly higher PASI 75 response rate than the 25 mg twice weekly group (p < 0.05, see figure below). The majority of patients who were initially randomised to 50 mg twice weekly and had their etanercept dose decreased at week 12 to 25 mg twice weekly maintained their PASI 75 response through week 36. For patients who received 25 mg twice weekly throughout the study, the PASI 75 response continued to improve between weeks 12 and 36.

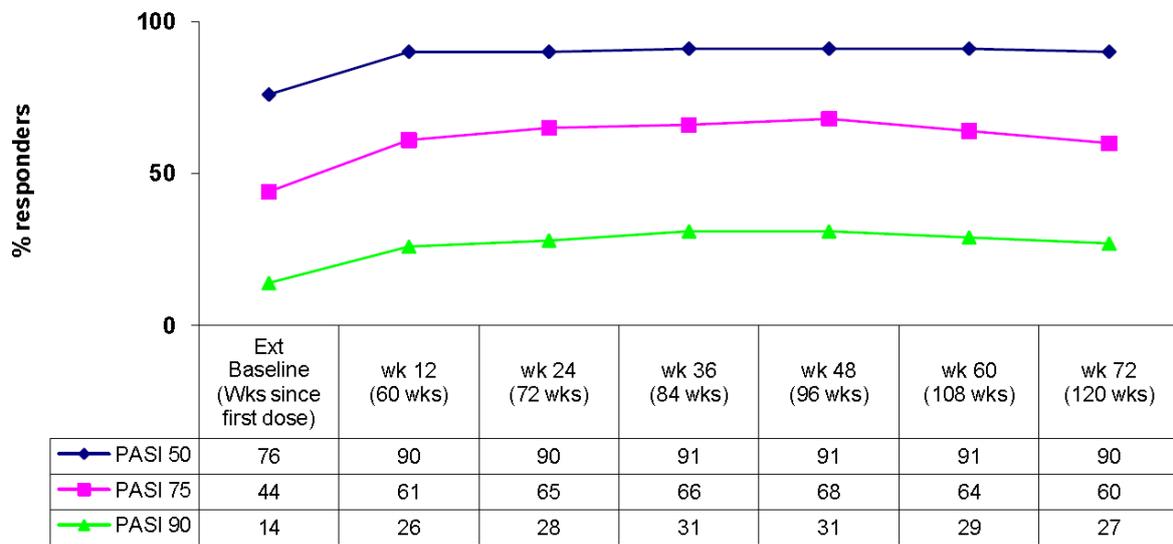
Figure 5. PASI 75 Response of Patients with Plaque Psoriasis in Study 2



x = $p < 0.001$ compared with placebo, y = $p < 0.05$ for 50 mg BIW compared with 25 mg BIW. p-values were only calculated for the double-blind period (up to week 12).

Subjects enrolled in either Study 1 or Study 2 (parent studies) were eligible to enter a phase III, open-label study to evaluate the long-term safety, tolerability, and maintenance of efficacy of etanercept in adults with plaque PsO. During the extension study, patients in one arm received etanercept 50 mg once weekly for 48 additional weeks (n=321).

Figure 6. PASI Responses of Patients with Plaque PsO Receiving Etanercept 50 mg Once Weekly in Extension Study#



PASI response percent responders from parent study baseline (LOCF) in patients receiving etanercept 50 mg once weekly.

Etanercept 50 mg once-weekly continued to provide durable efficacy as demonstrated by the percentage of subjects maintaining PASI 50, 75 and 90 responses over time. It was also well tolerated in this population and its safety profile was maintained throughout the extension study.

Immunocompetence

Evaluations of immunocompetence were performed on 49 etanercept-treated patients with active RA. No evidence of immunosuppression was found in evaluations of delayed-type hypersensitivity skin testing, enumeration of immune effector cell populations and immunoglobulins and in vitro testing of neutrophil and T cell function.

Antibodies

Antibodies to etanercept, all non-neutralising, were detected in 4 out of 96 RA patients who received etanercept at a dose of 25 mg twice a week for up to 3 months in a placebo-controlled trial. Results from JIA patients were similar to those seen in adult RA patients treated with etanercept. No apparent correlation of antibody development to clinical response or adverse events was seen. Of 98 patients with psoriatic arthritis who have been tested, no patient has developed antibodies to etanercept. Among 175 ankylosing spondylitis patients treated with etanercept, 3 patients were reported with antibodies to etanercept, none were neutralising. In double-blind studies up to 6 months duration in plaque psoriasis, about 1% of the 1,084 patients developed antibodies to etanercept, none were neutralising.

Comparative Efficacy of Brenzys and Enbrel®

The efficacy, safety / tolerability, and immunogenicity of Brenzys and EU Enbrel® were assessed in patients with moderate to severe RA despite MTX therapy (Study SB4-G31-RA).

The study evaluated 596 patients who were 18-75 years old with moderate to severe active disease despite MTX therapy. Patients were randomised in a 1:1 ratio to receive either Brenzys 50 mg (n=299) or EU Enbrel® 50 mg (n=297) once-weekly via subcutaneous injection. Patients

were enrolled in the study and followed up for up to 56 weeks after Randomisation, consisting of 52 weeks of active treatment and 4 weeks of safety follow-up.

The primary objective was to demonstrate equivalence of Brenzys and EU Enbrel® at Week 24 in terms of the American College of Rheumatology 20% response criteria (ACR20). To declare the equivalence between the treatment groups, the 2-sided 95% confidence interval of the difference in ACR20 response rates between the treatment groups should be contained within the pre-defined equivalence margin of [-15%, 15%]. Secondary objectives were to evaluate efficacy using relevant efficacy endpoints other than ACR20 at Weeks 24, and to evaluate safety / tolerability, PK, and immunogenicity of Brenzys compared to EU Enbrel®. In addition, steady-state PK of Brenzys and EU Enbrel® was evaluated.

The ACR20 response rates at Week 24 were equivalent for Brenzys and EU Enbrel® in the per-protocol set 1 (PPS1). The proportion of patients achieving ACR20 response in the PPS1 was 78.1% (193/247) and 80.5% (190/236) in the Brenzys and EU Enbrel® treatment groups, respectively. Furthermore, with non-responder imputation, the ACR20 response rates of Brenzys and EU Enbrel® were equivalent at Week 24 for the full analysis set; 73.6% of the Brenzys patients and 71.1% of the EU Enbrel® patients achieved the ACR20 response rate at Week 24.

The analysis of ACR20, ACR50 and ACR70 is shown in Table 15.

Table 15. Analysis of ACR Response Rates; Per-protocol Set (Study SB4-G31-RA)

ACR Response	Timepoint	Treatment	n/n'	(%)	Adjusted Difference Rate	95% CI
ACR20	Week 24 ^a	Brenzys 50 mg (N=247)	193/247	(78.1)	-2.37%	-9.54%, 4.80%
		Enbrel® 50 mg (N=236)	190/236	(80.5)		
	Week 52 ^b	Brenzys 50 mg (N=224)	181/224	(80.8)	-0.74%	-8.03%, 6.56%
		Enbrel® 50 mg (N=216)	176/216	(81.5)		
ACR50	Week 24 ^a	Brenzys 50 mg (N=247)	114/247	(46.2)	4.36%	-4.33%, 13.05%
		Enbrel® 50 mg (N=236)	100/236	(42.4)		
	Week 52 ^b	Brenzys 50 mg (N=224)	131/224	(58.5)	4.50%	-4.67%, 13.67%
		Enbrel® 50 mg (N=216)	115/216	(53.2)		
ACR70	Week 24 ^a	Brenzys 50 mg (N=247)	63/247	(25.5)	3.29%	-4.18%, 10.76%
		Enbrel® 50 mg (N=236)	53/236	(22.5)		
	Week 52 ^b	Brenzys 50 mg (N=224)	84/224	(37.5)	7.02%	-1.69%, 15.74%
		Enbrel® 50 mg (N=216)	67/216	(31.0)		

ACR20 = American College of Rheumatology 20% response criteria

ACR50 = American College of Rheumatology 50% response criteria

ACR70 = American College of Rheumatology 70% response criteria

CI = confidence interval; N = number of patients in the per-protocol set 1 or 2; n' = number of patients with an assessment; n = number of responders.

Per-protocol set 1 (PPS1) = PPS1 consisted of all full analysis set 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 Brenzys 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. Major PDs that led to exclusion from this set were pre-specified prior to unblinding the treatment codes for analyses.

Per-protocol set 2 (PPS2) = PPS2 consisted of all full analysis set patients who completed the Week 52 visit and had an adherence (from baseline to Week 52) within the range 80-120% of both the expected number of Brenzys or Enbrel® injections and the expected sum of MTX doses without any major PDs that affected the efficacy assessment. Percentages were based on the number of patients in the per-protocol set 1 or per-protocol set 2.

^a The ACR20/50/70 response rates at Week 24 were based on per-protocol set 1.

^b The ACR20/50/70 response rates at Week 52 were based on per-protocol set 2.

Change in the disease activity score based on a 28 joint count (DAS28) from baseline at Week 24 and Week 52 was also comparable between the treatment groups. The change in DAS28 from baseline at Week 24 was 2.5697 in the Brenzys treatment group and 2.5037 in the EU Enbrel® treatment group. The mean change in DAS28 score from baseline at Week 52 was 2.9108 in the Brenzys treatment group and 2.7990 in the EU Enbrel® treatment group.

The comparability of Brenzys and EU Enbrel® was further demonstrated in change from baseline in structural joint damage at Week 52 (Table 16).

Table 16. Summary of Structural Joint Damage; 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 patients in the full analysis set; n = number of completers with available radiographic assessment results at Week 0 and Week 52; SD = standard deviation.

Full Analysis Set (FAS) = FAS consisted of all patients who were randomised at the Randomisation Visit. Following the intent-to-treat principle, patients were analysed according to the treatment they were assigned at randomisation. However, patients who did not qualify for randomisation and were inadvertently randomised into the study were excluded from the FAS, provided these patients did not receive any Brenzys or Enbrel® during that study phase.

Following the 52-week randomised, double blind period (Study SB4-G31-RA), the long-term efficacy, safety / tolerability, and immunogenicity of Brenzys were assessed in RA patients treated previously with Brenzys or Enbrel®. A total of 126 patients from Brenzys treatment group were continued to receive Brenzys (Brenzys/Brenzys) and 119 patients from Enbrel® treatment group were switched to Brenzys (Enbrel®/Brenzys) in the open-label, extension period (Week 52 to Week 104).

The period consisted of 48 weeks of active treatment (Brenzys 50 mg once-weekly SC injection) and 4 weeks of safety follow-up.

The ACR response rates from Week 52 up to Week 100 were comparable between Brenzys/Brenzys and Enbrel®/Brenzys treatment groups.

The analysis of ACR20 response rates from Week 52 up to Week 100 are shown in the Table 17. The efficacy of treatment was similar after patients were switched from Enbrel® to Brenzys.

Table 17. ACR20 Response Rates from Week 52 up to Week 100; Extended Population (Study SB4-G31-RA)

Timepoint	Brenzys/Brenzys	Enbrel®/Brenzys	Total
	N=126	N=119	N=245
	n/n' (%)	n/n' (%)	n/n' (%)
Week 52	99/125 (79.2)	98/119 (82.4)	197/244 (80.7)
Week 76	102/125 (81.6)	90/117 (76.9)	192/242 (79.3)

Timepoint	Brenzys/Brenzys N=126 n/n' (%)	Enbrel®/Brenzys N=119 n/n' (%)	Total N=245 n/n' (%)
Week 100	95/122 (77.9)	91/115 (79.1)	186/237 (78.5)

N = number of patients in extended population; n' = number of patients with available assessment results at each timepoint.

Extended Population = Extended population consisted of all enrolled patients who had completed Week 52 treatment of the randomised, double-blind period, and who had received at least one dose of Brenzys in the open-label extension period.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Etanercept is slowly absorbed from the site of subcutaneous (SC) injection, reaching maximum concentration between 24 and 96 hours after a single dose. The absolute bioavailability is 76% as calculated in a population pharmacokinetic analysis of several studies. With twice weekly doses, it is anticipated that steady-state concentrations may be two to five-fold greater than those observed after single doses. After a single SC dose of 25 mg etanercept, the average maximum serum concentration observed in healthy volunteers was 1.65 ± 0.66 mg/L, and area under the curve was 235 ± 96.6 mg.hr/L. Dose proportionality has not been formally evaluated, but there is no apparent saturation of clearance across the dosing range.

Distribution

A bi-exponential curve is required to describe the concentration time curve of etanercept. The central volume of distribution of etanercept is 7.6 L, while the volume of distribution at steady state is 10.4 L.

After continued dosing of RA patients (n = 25) with etanercept for 6 months with 25 mg twice weekly, the median observed level was 3.0 mg/L (range 1.7 to 5.6 mg/L).

Excretion

Etanercept is cleared slowly from the body. The half-life is approximately 80 hours. Clearance is approximately 0.066 L/hr in patients with RA, somewhat lower than the value of 0.11 L/hr observed in healthy volunteers. Additionally, the pharmacokinetics of etanercept in rheumatoid arthritis patients, plaque psoriasis and ankylosing spondylitis patients are similar.

Serum concentration profiles at steady state were comparable among patients with RA treated with 50 mg etanercept powder for injection once weekly and those treated with 25 mg etanercept (Enbrel®) powder for injection twice weekly. A single 50 mg/mL injection of etanercept was also found to be bioequivalent to two simultaneous injections of 25 mg/mL. 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 (Enbrel®) twice weekly (n = 16). Serum concentrations in patients with RA have not been measured for periods of dosing that exceed 6 months. In an open-label, single-dose, two treatment crossover study in healthy volunteers, etanercept administered as a single injection of etanercept 50 mg solution for injection was found to be bioequivalent to two simultaneous injections of etanercept 25 mg (Enbrel®) powder for injection. The mean (\pm standard deviation) C_{max} and $AUC_{(0-T)}$ are expressed in Table 18.

Table 18. Summary of Pharmacokinetic Parameters after a Single Dose of Etanercept 50 mg Solution and Two Simultaneous Injections of Etanercept 25 mg Powder

	AUC_{0-t} (mg.h/L)	C_{max} (mg/L)
1 x Enbrel® 50 mg solution SC (n=33)	535 ± 192	3.90 ± 1.49
2 x Enbrel® 25 mg powder SC (n=33)	590 ± 208	4.09 ± 1.65

Point Estimate (%) 90% CI	91.3 (80.9, 103.1)	96.8 (84.1, 111.3)
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Although there is elimination of radioactivity in urine after administration of radiolabelled etanercept to patients and volunteers, increased etanercept concentrations were not observed in patients with acute renal or hepatic failure. The presence of renal and hepatic impairment should not require a change in dosage. There is no apparent pharmacokinetic difference between men and women.

No formal pharmacokinetic studies have been conducted to examine the metabolism of etanercept or the effects of renal or hepatic impairment. Methotrexate has no effect on the pharmacokinetics of etanercept. The effect of etanercept on the human pharmacokinetics of methotrexate has not been investigated.

The data described above were derived from studies using etanercept manufactured using a serum-based process.

Special populations

Elderly (>65 years)

The impact of advanced age was studied in the population pharmacokinetic analysis of etanercept serum concentrations. Clearance and volume estimates in patients aged 65 to 87 years were similar to estimates in patients less than 65 years of age.

Comparability of Brenzys with Enbrel® – Pharmacokinetic Properties

The pharmacokinetic profiles of Brenzys and Enbrel® were comparable in healthy volunteers following SC administration in a randomised, single-blind, cross-over study. Furthermore, equivalence of Brenzys and Enbrel® was demonstrated from supportive PK data generated from the clinical Phase III study.

The summary of the pharmacokinetic profiles of Brenzys, EU Enbrel® and US Enbrel® in healthy volunteers are listed in Table 19 and Table 20.

In supportive PK data obtained from RA patients, C_{trough} levels were comparable at each time point between Brenzys (ranging from 2.419 to 2.886 µg/mL in Weeks 2 to 24) and EU Enbrel® (ranging from 2.066 to 2.635 µg/mL in Weeks 2 to 24).

The AUC_{r} at Week 8 was 676.4 vs. 520.9 µg·h/mL and the inter-subject variability (CV%) was 37.7% vs. 50.1% in Brenzys and EU Enbrel®, respectively. The mean C_{max} at Week 8 was 5.1 ± 1.8 µg/mL and 4.1 ± 2.1 µg/mL in the Brenzys and EU Enbrel® treatment groups, respectively and the mean C_{min} was 2.6 ± 1.4 µg/mL and 1.8 ± 1.1 µg/mL in the Brenzys and EU Enbrel® treatment groups, respectively.

Table 19. Statistical Comparison of Primary PK Parameters (Brenzys vs. EU Enbrel®) (Study SB4-G11-NHV)

	Treatment	N	n	Geometric LSMeans	Ratio A/B	90% CI of Ratio	Intra-CV%
AUC_{last} (µg·h/mL)	Brenzys	45	42	688.853	0.986	0.942; 1.033	12.603
	EU Enbrel®	45	42	698.494			
AUC_{inf} (µg·h/mL)	Brenzys	45	42	729.371	0.990	0.947; 1.036	12.221
	EU Enbrel®	45	42	736.391			
C_{max} (µg/mL)	Brenzys	45	42	3.319	1.037	0.985; 1.092	14.205
	EU Enbrel®	45	42	3.201			

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; CI: confidence interval; C_{max} : maximum concentration; CV%: coefficient of variation; LSMeans: least squares means. Three subjects were excluded due to carryover effect.

Table 20. Statistical Comparison of Primary PK Parameters (Brenzys vs. US Enbrel®) (Study SB4-G11-NHV)

	Treatment	N	n	Geometric LSMeans	Ratio A/B	90% CI of Ratio	Intra-CV%
AUC _{last} (µg·h/mL)	Brenzys	45	44	749.543	1.010	0.954; 1.069	15.971
	US Enbrel®	45	44	742.437			
AUC _{inf} (µg·h/mL)	Brenzys	45	44	794.463	1.011	0.958; 1.067	15.220
	US Enbrel®	45	44	785.891			
C _{max} (µg/mL)	Brenzys	45	44	3.613	1.044	0.977; 1.114	18.406
	US Enbrel®	45	44	3.463			

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; CI: confidence interval; C_{max}: maximum concentration; CV%: coefficient of variation; LSMeans: least squares means. One subject was excluded due to carryover effect.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Genotoxicity studies showed no evidence of gene mutations or chromosomal damage.

Carcinogenicity

Etanercept studies in animals have not been conducted to evaluate the carcinogenic potential of etanercept.

Refer to Section 4.4 Special warnings and precautions for use.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Brenzys solution for injection also contains sucrose, sodium chloride, sodium phosphate monobasic monohydrate, sodium phosphate dibasic (heptahydrate) and water.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Solution for injection (Pre-filled syringe and Auto-injector)

Store at 2°C to 8°C. Refrigerate. Do not freeze. May be stored at temperatures up to a maximum of 25°C for a single period of up to 4 weeks. Brenzys should be discarded if exposed to high temperatures, or if not used within 4 weeks of initial removal from refrigeration.

Keep the pre-filled syringes and the Auto-injectors in the outer carton in order to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Pre-filled syringe (solution for injection)

Brenzys solution for injection is supplied in a kit containing 4 single-dose pre-filled glass syringes with stainless steel needle, rubber needle cover not made with natural rubber latex,

and plastic plunger containing Brenzys solution. Each syringe of Brenzys contains 50 mg (in 1 mL) of the active ingredient, etanercept.

Auto-injector (solution for injection)

The Brenzys pre-filled auto-injector contains 50 mg of etanercept. The auto-injector consists of a syringe made from clear Type 1 glass with a 27 gauge needle, rubberneedle cover not made with natural rubber latex, and plastic plunger. Each Carton contains either 1 or 4 Brenzys auto-injectors.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Etanercept is a human tumour necrosis factor receptor p75 Fc fusion protein produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian expression system. Etanercept is a dimer of a protein genetically engineered by fusing the extracellular ligand-binding domain of human tumour necrosis factor receptor-2 (TNFR2/p75) to the Fc domain of human IgG1. This Fc component contains the hinge, CH2 and CH3 regions but not the CH1 region of IgG1. Etanercept contains 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons. Etanercept is now manufactured using a serum-free process.

The potency is determined by measuring the ability of etanercept to neutralise the TNF α -mediated growth inhibition of A375 cells. The specific activity of etanercept is 1.7x10⁶ units/mg.

CAS number

CAS Registry Number: 185243-69-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Sponsor:

SAMSUNG BIOEPIS AU PTY LTD
Level 16, 201 Elizabeth Street,
Sydney NSW 2000, Australia

Distributor:

Merck Sharp & Dohme (Australia) Pty Ltd
Level 1, Building A, 26 Talavera Road,
Macquarie Park NSW 2113, Australia
<http://www.msd-australia.com.au>
Tel (61) 02 8988 8000

9 DATE OF FIRST APPROVAL

22 July 2016

10 DATE OF REVISION

20 November 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.8 ADVERSE EFFECTS	Added “bleeding, bruising” as very common reactions, in the table of Adverse Reactions,