fibrosis and pneumonia died due to respiratory failure. Two percent of patients treated concurrently with etanercept and anakinra developed neutropenia (ANC < 1 x 10^9/L).

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 *[see Warnings and Precautions (5.12)]*.

7.3 Cyclophosphamide

The use of ERELZI in patients receiving concurrent cyclophosphamide therapy is not recommended *[see Warnings and Precautions (5.11)]*.

7.4 Sulfasalazine

Patients in a clinical study who were on established therapy with sulfasalazine, to which etanercept was added, were noted to develop a mild decrease in mean neutrophil counts in comparison to groups treated with either etanercept or sulfasalazine alone. The clinical significance of this observation is unknown.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available studies with use of etanercept during pregnancy do not reliably support an association between etanercept and major birth defects. Clinical data are available from the Organization of Teratology Information Specialists (OTIS) Pregnancy Registry in women with rheumatic diseases or another indication and a Scandinavian study in pregnant women with chronic inflammatory disease. Both the OTIS Registry and the Scandinavian study showed the proportion of liveborn infants with major birth defects was higher for women exposed to etanercept compared to diseased etanercept unexposed women. However, the lack of pattern of major birth defects is reassuring and differences between exposure groups (e.g. disease severity) may have impacted the occurrence of birth defects *[see Data]*. In animal reproduction studies with pregnant rats and rabbits, no fetal harm or malformations were observed with subcutaneous administration of etanercept during the period of organogenesis at doses that achieved systemic exposures 48 to 58 times the exposure in patients treated with 50 mg etanercept once weekly *[see Data]*.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the United States, about 2-4% of liveborn babies have a major birth defect and about 15-20% of pregnancies end in miscarriage, regardless of drug exposure.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

The risk of fetal/neonatal adverse reactions with in utero exposure to etanercept is unknown. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to etanercept in utero *[see Use in Specific Populations (8.4)]*.

Data

Human Data

A prospective cohort pregnancy registry conducted by OTIS in the US and Canada between 2000 and 2012 compared the risk of major birth defects in liveborn infants of women with rheumatic diseases or another indication exposed to etanercept in the first trimester. The proportion of major birth defects among liveborn infants in the etanercept-exposed (N = 319) and diseased etanercept unexposed cohorts (N = 144) was 9.4% and 3.5%, respectively. The findings showed no statistically significant increased risk of minor birth defects and no pattern of major or minor birth defects.

A Scandinavian study compared the risk of major birth defects in liveborn infants of women with chronic inflammatory disease (CID) exposed to TNF-inhibitors during early pregnancy. Women were identified from the Danish (2004-2012) and Swedish (2006-2012) population based health registers. The proportion of major birth defects among liveborn infants in the etanercept-exposed (N=344) and CID etanercept unexposed cohorts (N = 21,549) was 7.0% and 4.7%, respectively.

Overall, while both the OTIS Registry and Scandinavian study show a higher proportion of major birth defects in etanercept-exposed patients compared to diseased etanercept unexposed patients, the lack of pattern of birth defects is reassuring and differences between exposure groups (e.g. disease severity) may have impacted the occurrence of birth defects.

Three case reports from the literature showed that cord blood levels of etanercept at delivery, in infants born to women administered etanercept during pregnancy, were between 3% and 32% of the maternal serum level.

Animal Data

In embryofetal development studies with etanercept administered during the period of organogenesis to pregnant rats from gestation day (GD) 6 through 20 or pregnant rabbits from GD 6 through 18, there was no evidence of fetal malformations or embryotoxicity in rats or rabbits at respective doses that achieved systemic exposures 48 to 58 times the exposure in patients treated with 50 mg etanercept once weekly (on an AUC basis with maternal subcutaneous doses up to 30 mg/kg/day in rats and 40 mg/kg/day in rabbits). In a peri-and post-natal development study with pregnant rats that received etanercept during organogenesis and the later gestational period from GD 6 through 21, development of pups through post-natal day 4 was unaffected at doses that achieved exposures 48 times the exposure in patients treated with 50 mg etanercept once weekly (on an AUC basis with maternal subcutaneous doses up to 30 mg/kg/day).

8.2 Lactation

Risk Summary

Limited data from published literature show that etanercept is present in low levels in human milk and minimally absorbed by a breastfed infant. No data are available on the effects of etanercept on the breastfed child or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ERELZI and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

8.4 Pediatric Use
Etanercept has been studied in 69 children with moderately to severely active polyarticular JIA aged 2 to 17 years.

Etanercept has not been studied in children < 2 years of age with JIA. For pediatric specific safety information concerning malignancies and inflammatory bowel disease, *[see Warnings and Precautions (5.3) and Adverse Reactions (6.2)]*.

The clinical significance of infant exposure to etanercept *in utero* is unknown. The safety of administering live or live-attenuated vaccines in exposed infants is unknown. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to exposed infants. For pediatric specific safety information concerning vaccinations *[see Warnings and Precautions (5.8) and Drug Interactions (7.1)]*.

8.5 Geriatric Use
A total of 480 RA patients ages 65 years or older have been studied in clinical trials. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

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

10 OVERDOSAGE
No dose-limiting toxicities have been observed during clinical trials of etanercept. Single IV doses up to 60 mg/m^2 (approximately twice the recommended dose) have been administered to healthy volunteers in an endotoxemia study without evidence of dose-limiting toxicities.

11 DESCRIPTION
ERELZI (etanercept-szzs), a tumor necrosis factor (TNF) blocker, is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) tumor necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1. The Fc component of etanercept-szzs contains the C_H2 domain, the C_H3 domain and hinge region, but not the C_H1 domain of IgG1. Etanercept-szzs is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system. It consists of 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons.

ERELZI (etanercept-szzs) Injection in the single-dose prefilled syringe with BD UltraSafe Passive Needle Guard and the single-dose prefilled Sensoready Pen is clear and colorless to slightly yellow, sterile, preservative-free, and is formulated at pH 6.3 ± 0.2. ERELZI is for subcutaneous use.

Table 5. Contents of ERELZI

Presentation	Active Ingredient Content	Inactive Ingredients Content
Etanercept-szzs 50 mg prefilled syringe with BD UltraSafe Passive Needle Guard and Sensoready Pen	50 mg etanercept-szzs in 1 mL	0.786 mg citric acid 13.52 mg sodium citrate 1.5 mg sodium chloride 10 mg sucrose 4.6 mg lysine
Etanercept-szzs 25 mg prefilled syringe with BD UltraSafe Passive Needle Guard	25 mg etanercept-szzs in 0.5 mL	0.393 mg citric acid 6.76 mg sodium citrate 0.75 mg sodium chloride 5 mg sucrose 2.3 mg lysine

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. It plays an important role in the inflammatory processes of RA, polyarticular JIA, AS, and another indication and the resulting joint pathology. Elevated levels of TNF are found in involved tissues and fluids of patients with RA, JIA, AS, and two other indications.

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 products are dimeric soluble forms of the p75 TNF receptor that can bind TNF molecules. Etanercept products inhibit binding of TNF-α and TNF-β (lymphotoxin alpha [LT-α]) to cell surface TNFRs, rendering TNF biologically inactive. In *in vitro* studies, large complexes of etanercept with TNF-α were not detected and cells expressing transmembrane TNF (that binds etanercept products) are not lysed in the presence or absence of complement.

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

After administration of 25 mg of etanercept by a single SC injection to 25 patients with RA, a mean ± standard deviation half-life of 102 ± 30 hours was observed with a clearance of 160 ± 80 mL/hr. A maximum serum concentration (C_{max}) of 1.1 ± 0.6 mcg/mL and time to C_{max} of 69 ± 34 hours was observed in these patients following a single 25 mg dose. After 6 months of twice weekly 25 mg doses in these same RA patients, the mean C_{max} was 2.4 ± 1.0 mcg/mL (N = 23).

Patients exhibited a 2- to 7-fold increase in peak serum concentrations and approximately 4-fold increase in $AUC_{0\text{-}72\ hr}$ (range 1- to 17-fold) with repeated dosing. Serum concentrations in patients with RA have not been measured for periods of dosing that exceed 6 months.

In another study, serum concentration profiles at steady-state were comparable among patients with RA treated with 50 mg etanercept once weekly and those treated with 25 mg etanercept twice weekly. The mean (± standard deviation) C_{max}, C_{min}, and partial AUC were 2.4 ± 1.5 mcg/mL, 1.2 ± 0.7 mcg/mL, and 297 ± 166 mcg•h/mL, respectively, for patients treated with 50 mg etanercept once weekly (N = 21); and 2.6 ± 1.2 mcg/mL, 1.4 ± 0.7 mcg/mL, and 316 ± 135 mcg•h/mL for patients treated with 25 mg etanercept twice weekly (N = 16).

Patients with JIA (ages 4 to 17 years) were administered 0.4 mg/kg of etanercept twice weekly (up to a maximum dose of 50 mg per week) for up to 18 weeks. The mean serum concentration after repeated SC dosing was 2.1 mcg/mL, with a range of 0.7 to 4.3 mcg/mL. Limited data suggest that the clearance of etanercept is reduced slightly in children ages 4 to 8 years. Population pharmacokinetic analyses predict that the pharmacokinetic differences between the regimens of 0.4 mg/kg twice weekly and 0.8 mg/kg once weekly in JIA patients are of the same magnitude as the differences observed between twice weekly and weekly regimens in adult RA patients.

In clinical studies with etanercept, pharmacokinetic parameters were not different between men and women and did not vary with age in adult patients. The pharmacokinetics of etanercept were unaltered by concomitant MTX in RA patients. No formal pharmacokinetic studies have been conducted to examine the effects of renal or hepatic impairment on etanercept disposition.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES

14.1 Adult Rheumatoid Arthritis

The safety and efficacy of etanercept were assessed in four randomized, double-blind, controlled studies. The results of all four trials were expressed in percentage of patients with improvement in RA using ACR response criteria.

Study I evaluated 234 patients with active RA who were ≥ 18 years old, had failed therapy with at least one but no more than four disease-modifying antirheumatic drugs (DMARDs) (e.g., hydroxychloroquine, oral or injectable gold, MTX, azathioprine, D-penicillamine, sulfasalazine), and had ≥ 12 tender joints, ≥ 10 swollen joints, and either erythrocyte sedimentation rate (ESR) ≥ 28 mm/hr, C-reactive protein (CRP) > 2.0 mg/dL, or morning stiffness for ≥ 45 minutes. Doses of 10 mg or 25 mg etanercept or placebo were administered SC twice a week for 6 consecutive months.

Study II evaluated 89 patients and had similar inclusion criteria to Study I except that patients in Study II had additionally received MTX for at least 6 months with a stable dose (12.5 to 25 mg/week) for at least 4 weeks and they had at least 6 tender or painful joints. Patients in Study II received a dose of 25 mg etanercept or placebo SC twice a week for 6 months in addition to their stable MTX dose.

Study III compared the efficacy of etanercept to MTX in patients with active RA. This study evaluated 632 patients who were ≥ 18 years old with early (≤ 3 years disease duration) active RA, had never received treatment with MTX, and had ≥ 12 tender joints, ≥ 10 swollen joints, and either ESR ≥ 28 mm/hr, CRP > 2.0 mg/dL, or morning stiffness for ≥ 45 minutes. Doses of 10 mg or 25 mg etanercept were administered SC twice a week for 12 consecutive months. The study was unblinded after all patients had completed at least 12 months (and a median of 17.3 months) of therapy. The majority of patients remained in the study on the treatment to which they were randomized through 2 years, after which they entered an extension study and received open-label 25 mg etanercept. MTX tablets (escalated from 7.5 mg/week to a maximum of 20 mg/week over the first 8 weeks of the trial) or placebo tablets were given once a week on the same day as the injection of placebo or etanercept doses, respectively.

Study IV evaluated 682 adult patients with active RA of 6 months to 20 years duration (mean of 7 years) who had an inadequate response to at least one DMARD other than MTX. Forty-three percent of patients had previously received MTX for a mean of 2 years prior to the trial at a mean dose of 12.9 mg. Patients were excluded from this study if MTX had been discontinued for lack of efficacy or for safety considerations. The patient baseline characteristics were similar to those of patients in Study I. Patients were randomized to MTX alone (7.5 to 20 mg weekly, dose escalated as described for Study III; median dose 20 mg), etanercept alone (25 mg twice weekly), or the combination of etanercept and MTX initiated concurrently (at the same doses as above). The study evaluated ACR response, Sharp radiographic score, and safety.

Clinical Response

A higher percentage of patients treated with etanercept and etanercept in combination with MTX achieved ACR 20, ACR 50, and ACR 70 responses and Major Clinical Responses than in the comparison groups. The results of Studies I, II, and III are summarized in **Table 6**. The results of Study IV are summarized in **Table 7**.

Table 6. ACR Responses in Placebo- and Active-Controlled Trials (Percent of Patients)

Response	Placebo Controlled				Active Controlled	
	Study I		Study II		Study III	
	Placebo N=80	Etanercept[a] N= 78	MTX/Placebo N= 30	MTX/Etanercept[a] N= 59	MTX N= 217	Etanercept[a] N= 207
ACR 20						
Month 3	23%	62%	33%	66%	56%	62%
Month 6	11%	59%	27%	71%	58%	65%
Month 12	NA	NA	NA	NA	65%	72%
ACR 50						
Month 3	8%	41%	0%	42%	24%	29%
Month 6	5%	40%	3%	39%	32%	40%
Month 12	NA	NA	NA	NA	43%	49%
ACR 70						
Month 3	4%	15%	0%	15%	7%	13%
Month 6	1%	15%	0%	15%	14%	21%
Month 12	NA	NA	NA	NA	22%	25%

[a] 25 mg etanercept SC twice weekly
[b] $p < 0.01$, etanercept vs placebo
[c] $p < 0.05$, etanercept vs MTX

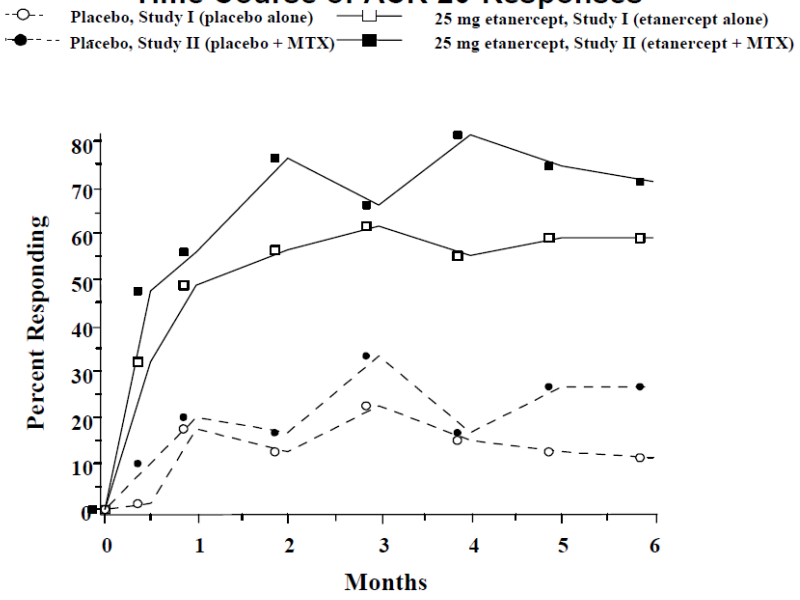
Table 7. Study IV Clinical Efficacy Results: Comparison of MTX vs Etanercept vs Etanercept in Combination With MTX in Patients With Rheumatoid Arthritis of 6 Months to 20 Years Duration (Percent of Patients)

Endpoint	MTX (N= 228)	Etanercept (N= 223)	Etanercept/MTX (N= 231)
ACR N[a,b]			
Month 12	40%	47%	63%[c]
ACR 20			
Month 12	59%	66%	75%[c]
ACR 50			
Month 12	36%	43%	63%[c]
ACR 70			
Month 12	17%	22%	40%[c]
Major Clinical Response[d]	6%	10%	24%[c]

[a] Values are medians.
[b] ACR N is the percent improvement based on the same core variables used in defining ACR 20, ACR 50, and ACR 70.
[c] $p < 0.05$ for comparisons of etanercept/MTX vs etanercept alone or MTX alone.
[d] Major clinical response is achieving an ACR 70 response for a continuous 6-month period.

The time course for ACR 20 response rates for patients receiving placebo or 25 mg etanercept in Studies I and II is summarized in Figure 1. The time course of responses to etanercept in Study III was similar.

Figure 1:
Time Course of ACR 20 Responses



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 in Studies I and III: 25 mg etanercept was more effective than 10 mg (10 mg was not evaluated in Study II). Etanercept was significantly better than placebo in all components of the ACR criteria as well as other measures of RA disease activity not included in the ACR response criteria, such as morning stiffness.

In Study III, ACR response rates and improvement in all the individual ACR response criteria were maintained through 24 months of etanercept therapy. Over the 2-year study, 23% of etanercept's patients achieved a major clinical response, defined as maintenance of an ACR 70 response over a 6-month period.

The results of the components of the ACR response criteria for Study I are shown in **Table 8**. Similar results were observed for etanercept -treated patients in Studies II and III.

Table 8. Components of ACR Response in Study I

	Placebo N=80		Etanercept[a] N=78	
Parameter (median)	**Baseline**	**3 Months**	**Baseline**	**3 Months***
Number of tender joints[b]	34.0	29.5	31.2	10.0[f]
Number of swollen joints[c]	24.0	22.0	23.5	12.6[f]
Physician global assessment[d]	7.0	6.5	7.0	3.0[f]
Patient global assessment[d]	7.0	7.0	7.0	3.0[f]
Pain[d]	6.9	6.6	6.9	2.4[f]
Disability index[e]	1.7	1.8	1.6	1.0[f]
ESR (mm/hr)	31.0	32.0	28.0	15.5[f]
CRP (mg/dL)	2.8	3.9	3.5	0.9[f]

*Results at 6 months showed similar improvement.
[a]25 mg etanercept SC twice weekly.
[b]Scale 0-71.
[c]Scale 0-68.
[d]Visual analog scale: 0 = best; 10 = worst.
[e]Health Assessment Questionnaire: 0 = best; 3 = worst; includes eight categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.
[f]$p < 0.01$, etanercept vs placebo, based on mean percent change from baseline.

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

Continued durable responses were seen for over 60 months in open-label extension treatment trials when patients received etanercept without interruption. A substantial number of patients who initially received concomitant MTX or corticosteroids were able to reduce their doses or discontinue these concomitant therapies while maintaining their clinical responses.

Physical Function Response

In Studies I, II, and III, physical function and disability were assessed using the Health Assessment Questionnaire (HAQ). Additionally, in Study III, patients were administered the SF-36 Health Survey. In Studies I and II, patients treated with 25 mg etanercept twice weekly showed greater improvement from baseline in the HAQ score beginning in month 1 through month 6 in comparison to placebo ($p < 0.001$) for the HAQ disability domain (where 0 = none and 3 = severe). In Study I, the mean improvement in the HAQ score from baseline to month 6 was 0.6 (from 1.6 to 1.0) for the 25 mg etanercept group and 0 (from 1.7 to 1.7) for the placebo group. In Study II, the mean improvement from baseline to month 6 was 0.6 (from 1.5 to 0.9) for the etanercept /MTX group and 0.2 (from 1.3 to 1.2) for the placebo/MTX group. In Study III, the mean improvement in the HAQ score from baseline to month 6 was 0.7 (from 1.5 to 0.7) for

25 mg etanercept twice weekly. All subdomains of the HAQ in Studies I and III were improved in patients treated with etanercept.

In Study III, patients treated with 25 mg etanercept twice weekly showed greater improvement from baseline in SF-36 physical component summary score compared to etanercept 10 mg twice weekly and no worsening in the SF-36 mental component summary score. In open-label studies of etanercept, improvements in physical function and disability measures have been maintained for up to 4 years.

In Study IV, median HAQ scores improved from baseline levels of 1.8, 1.8, and 1.8 to 1.1, 1.0, and 0.6 at 12 months in the MTX, etanercept, and etanercept /MTX combination treatment groups, respectively (combination versus both MTX and etanercept, $p < 0.01$). Twenty-nine percent of patients in the MTX alone treatment group had an improvement of HAQ of at least 1 unit versus 40% and 51% in etanercept alone and etanercept /MTX combination treatment groups, respectively.

Radiographic Response

In Study III, 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 (JSN) score. Radiographs of hands/wrists and forefeet were obtained at baseline, 6 months, 12 months, and 24 months and scored by readers who were unaware of treatment group. The results are shown in Table 9. A significant difference for change in erosion score was observed at 6 months and maintained at 12 months.

Table 9. Mean Radiographic Change Over 6 and 12 Months in Study III

		MTX	**25 mg Etanercept**	**MTX/Etanercept (95% Confidence Interval*)**	**P Value**
12 Months	Total Sharp Score	1.59	1.00	0.59 (-0.12, 1.30)	0.1
	Erosion Score	1.03	0.47	0.56 (0.11, 1.00)	0.002
	JSN Score	0.56	0.52	0.04 (-0.39, 0.46)	0.5
6 Months	Total Sharp Score	1.06	0.57	0.49 (0.06, 0.91)	0.001
	Erosion Score	0.68	0.30	0.38 (0.09, 0.66)	0.001
	JSN Score	0.38	0.27	0.11 (-0.14, 0.35)	0.6

* 95% confidence intervals for the differences in change scores between MTX and etanercept.

Patients continued on the therapy to which they were randomized for the second year of Study III. Seventy-two percent of patients had x-rays obtained at 24 months. Compared to the patients in the MTX group, greater inhibition of progression in TSS and erosion score was seen in the 25 mg etanercept group, and, in addition, less progression was noted in the JSN score.

In the open-label extension of Study III, 48% of the original patients treated with 25 mg etanercept have been evaluated radiographically at 5 years. Patients had continued inhibition of structural damage, as measured by the TSS, and 55% of them had no progression of structural damage. Patients originally treated with MTX had further reduction in radiographic progression once they began treatment with etanercept.

In Study IV, less radiographic progression (TSS) was observed with etanercept in combination with MTX compared with etanercept alone or MTX alone at month 12 (Table 10). In the MTX treatment group, 55% of patients experienced no radiographic progression (TSS change ≤ 0.0) at 12 months compared to 63% and 76% in etanercept alone and etanercept /MTX combination treatment groups, respectively.

Table 10. Mean Radiographic Change in Study IV at 12 Months (95% Confidence Interval)

	MTX (N=212)	**Etanercept (N=212)***	**Etanercept/MTX (N=218)***
Total Sharp Score (TSS)	2.80	0.52[a]	-0.54[b,c]
	(1.08, 4.51)	(-0.10, 1.15)	(-1.00, -0.07)
Erosion Score (ES)	1.68	0.21[a]	-0.30[b]
	(0.61, 2.74)	(-0.20, 0.61)	(-0.65, 0.04)
Joint Space Narrowing (JSN) Score	1.12	0.32	-0.23[b,c]
	(0.34, 1.90)	(0.00, 0.63)	(-0.45, -0.02)

*Analyzed radiographic ITT population.

[a] $p < 0.05$ for comparison of etanercept vs MTX.

[b] $p < 0.05$ for comparison of etanercept/MTX vs MTX.

[c] $p < 0.05$ for comparison of etanercept/MTX vs etanercept.

Once Weekly Dosing

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. Fifty-three 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 groups were similar.

14.2 Polyarticular Juvenile Idiopathic Arthritis (JIA)

The safety and efficacy of etanercept were assessed in a 2-part study in 69 children with polyarticular JIA who had a variety of JIA onset types. Patients ages 2 to 17 years with moderately to severely active polyarticular JIA refractory to or intolerant of MTX were enrolled; patients remained on a stable dose of a single nonsteroidal anti-inflammatory drug and/or prednisone (≤ 0.2 mg/kg/day or 10 mg maximum). In part 1, all patients received 0.4 mg/kg (maximum 25 mg per dose) etanercept SC twice weekly. In part 2, patients with a clinical response at day 90 were randomized to remain on etanercept or receive placebo for 4 months and assessed for disease flare. Responses were measured using the JIA Definition of Improvement

(DOI), defined as ≥ 30% improvement in at least three of six and ≥ 30% worsening in no more than one of the six JIA core set criteria, including active joint count, limitation of motion, physician and patient/parent global assessments, functional assessment, and ESR. Disease flare was defined as a ≥ 30% worsening in three of the six JIA core set criteria and ≥ 30% improvement in not more than one of the six JIA core set criteria and a minimum of two active joints.

In part 1 of the study, 51 of 69 (74%) patients demonstrated a clinical response and entered part 2. In part 2, 6 of 25 (24%) patients remaining on etanercept experienced a disease flare compared to 20 of 26 (77%) patients receiving placebo ($p = 0.007$). From the start of part 2, the median time to flare was ≥ 116 days for patients who received etanercept and 28 days for patients who received placebo. Each component of the JIA core set criteria worsened in the arm that received placebo and remained stable or improved in the arm that continued on etanercept. The data suggested the possibility of a higher flare rate among those patients with a higher baseline ESR. Of patients who demonstrated a clinical response at 90 days and entered part 2 of the study, some of the patients remaining on etanercept continued to improve from month 3 through month 7, while those who received placebo did not improve.

The majority of JIA patients who developed a disease flare in part 2 and reintroduced etanercept treatment up to 4 months after discontinuation re-responded to etanercept therapy in open-label studies. Most of the responding patients who continued etanercept therapy without interruption have maintained responses for up to 48 months.

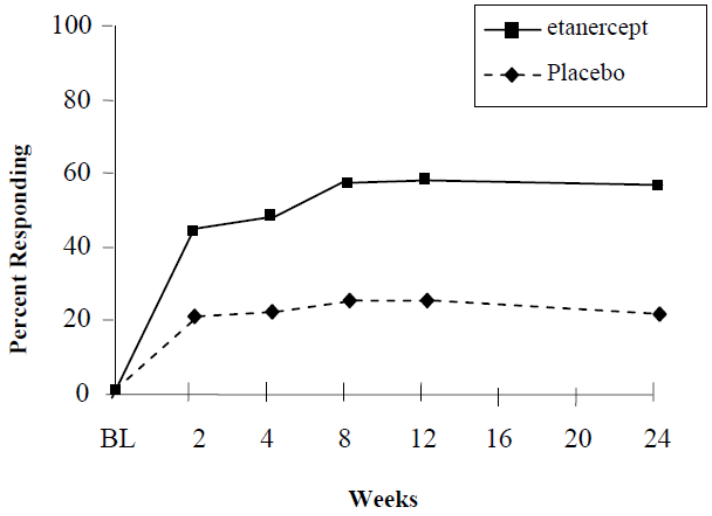
Studies have not been done in patients with polyarticular JIA to assess the effects of continued etanercept therapy in patients who do not respond within 3 months of initiating etanercept therapy, or to assess the combination of etanercept with MTX.

14.3 Ankylosing Spondylitis

The safety and efficacy of etanercept were assessed in a randomized, double-blind, placebo-controlled study in 277 patients with active AS. Patients were between 18 and 70 years of age and had AS as defined by the modified New York Criteria for Ankylosing Spondylitis. Patients were to have evidence of active disease based on values of ≥ 30 on a 0-100 unit Visual Analog Scale (VAS) for the average of morning stiffness duration and intensity, and two of the following three other parameters: a) patient global assessment, b) average of nocturnal and total back pain, and c) the average score on the Bath Ankylosing Spondylitis Functional Index (BASFI). Patients with complete ankylosis of the spine were excluded from study participation. Patients taking hydroxychloroquine, sulfasalazine, methotrexate, or prednisone (≤ 10 mg/day) could continue these drugs at stable doses for the duration of the study. Doses of 25 mg etanercept or placebo were administered SC twice a week for 6 months.

The primary measure of efficacy was a 20% improvement in the Assessment in Ankylosing Spondylitis (ASAS) response criteria. Compared to placebo, treatment with etanercept resulted in improvements in the ASAS and other measures of disease activity (Figure 2 and **Table 12**).

Figure 2. ASAS 20 Responses in Ankylosing Spondylitis



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 ($p \leq 0.0001$, etanercept vs placebo). Similar responses were seen at Week 24. Responses were similar between those patients receiving concomitant therapies at baseline and those who were not. The results of this study were similar to those seen in a single-center, randomized, placebo-controlled study of 40 patients and a multicenter, randomized, placebo-controlled study of 84 patients with AS.

Table 12. Components of Ankylosing Spondylitis Disease Activity

	Placebo N=139		Etanercept[a] N=138	
Median values at time points	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) with 0 = "none" and 100 = "severe".
[c] Average of total nocturnal and back pain scores, measured on a VAS 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.

15 REFERENCES

1. National Cancer Institute. Surveillance, Epidemiology, and End Results Database (SEER) Program. SEER Incidence Crude Rates, 13 Registries, 1992-2002.

16 HOW SUPPLIED/STORAGE AND HANDLING

Administration of one 50 mg ERELZI prefilled syringe with BD UltraSafe Passive Needle Guard or one ERELZI Sensoready Pen provides a dose equivalent to two 25 mg ERELZI prefilled syringes with BD UltraSafe Passive Needle Guard.

ERELZI Prefilled Syringe with BD UltraSafe Passive Needle Guard and ERELZI Prefilled Sensoready Pen

Each ERELZI (etanercept-szzs) Injection single-dose prefilled syringe with BD UltraSafe Passive Needle Guard and ERELZI single-dose prefilled Sensoready Pen contains clear and

colorless to slightly yellow solution containing 25 mg/0.5 mL or 50 mg/mL of etanercept-szzs in a single-dose syringe with a 27-gauge, ½-inch needle.

50 mg/mL single-dose prefilled syringe	Carton of 4	NDC 61314-821-04
50 mg/mL single-dose prefilled Sensoready Pen	Carton of 4	NDC 61314-832-04
25 mg/0.5 mL single-dose prefilled syringe	Carton of 4	NDC 61314-843-04

ERELZI should be refrigerated at 36°F to 46°F (2°C to 8°C). Do not use ERELZI beyond the expiration date stamped on the carton or barrel label. DO NOT SHAKE. Store ERELZI in the original carton to protect from light or physical damage.

For convenience, storage of individual syringes or Sensoready Pens at room temperature between 68°F to 77°F (20°C to 25°C) for a maximum single period of 28 days is permissible, with protection from light and sources of heat. Once a syringe or Sensoready Pen has been stored at room temperature, it should not be placed back into the refrigerator. If not used within 28 days at room temperature, the syringe or Sensoready Pens should be discarded. Do not store ERELZI in extreme heat or cold. DO NOT FREEZE. Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read FDA-approved patient labeling *(Medication Guide and Instructions for Use)* before the patient starts using ERELZI, and each time the prescription is renewed, as there may be new information they need to know.

Patients or their caregivers should be provided the ERELZI "Medication Guide" and provided an opportunity to read it and ask questions prior to initiation of therapy. The healthcare provider should ask the patient questions to determine any risk factors for treatment. Patients developing signs and symptoms of infection should seek medical evaluation immediately.

Patient Counseling

Patients should be advised of the potential benefits and risks of ERELZI. Physicians should instruct their patients to read the Medication Guide before starting ERELZI therapy and to reread each time the prescription is renewed.

Infections

Inform patients that ERELZI may lower the ability of their immune system to fight infections. Advise patients of the importance of contacting their doctor if they develop any symptoms of infection, tuberculosis or reactivation of hepatitis B virus infections.

Other Medical Conditions

Advise patients to report any signs of new or worsening medical conditions, such as central nervous system demyelinating disorders, heart failure or autoimmune disorders, such as lupus-like syndrome or autoimmune hepatitis. Counsel about the risk of lymphoma and other

Instructions for Use

ERELZI (eh rel' zee)

(etanercept-szzs)

Prefilled Syringe

Important:

To help avoid a possible infection, you should follow these instructions.

Be sure that you read, understand, and follow this Instructions for Use before injecting ERELZI. Your healthcare provider should show you how to prepare and inject ERELZI properly using the prefilled syringe before you use it for the first time. Talk to your healthcare provider if you have any questions.

Important:

- **Do not use** the ERELZI prefilled syringe if the seal of the blister tray is broken.
- Keep the ERELZI prefilled syringe in the original carton to protect from light or damage until you are ready to use it.
- Inject ERELZI 15 to 30 minutes after taking it out of the refrigerator.
- **Do not shake** the ERELZI prefilled syringe.
- **The needle cap on the prefilled syringe contains latex. Do not handle the prefilled syringe if you are sensitive to latex.**
- The prefilled syringe has a needle guard that will be activated to cover the needle after the injection is given. The needle guard will help to prevent needle stick injuries to anyone who handles the prefilled syringe.
- Do not remove the needle cap until just before you give the injection.
- Avoid touching the needle guard wings before use. Touching them may cause the needle guard to be activated too early.
- Throw away (dispose of) the used ERELZI prefilled syringe right away after use. **Do not re-use a ERELZI prefilled syringe.** See **"How should I dispose of used ERELZI prefilled syringes?"** at the end of this Instructions for Use.

How should I store ERELZI?

- Store your carton of ERELZI prefilled syringes in the refrigerator, between 36°F to 46°F (2°C to 8°C).
- If needed, you may store the ERELZI prefilled syringe at room temperature between 68°F to 77°F (20°C to 25°C) for up to 28 days. Once the ERELZI prefilled syringe has reached room temperature, do not put it back into the refrigerator. Throw away the ERELZI prefilled syringe that has been stored at room temperature after 28 days.
- Keep ERELZI prefilled syringes in the original carton until ready to use to protect from light.
- Do not store ERELZI in extreme heat or cold such as in your vehicle's glove box or trunk.
- Do not freeze ERELZI prefilled syringes.

Keep ERELZI and all medicines out of the reach of children.

ERELZI prefilled syringe parts (see Figure A).

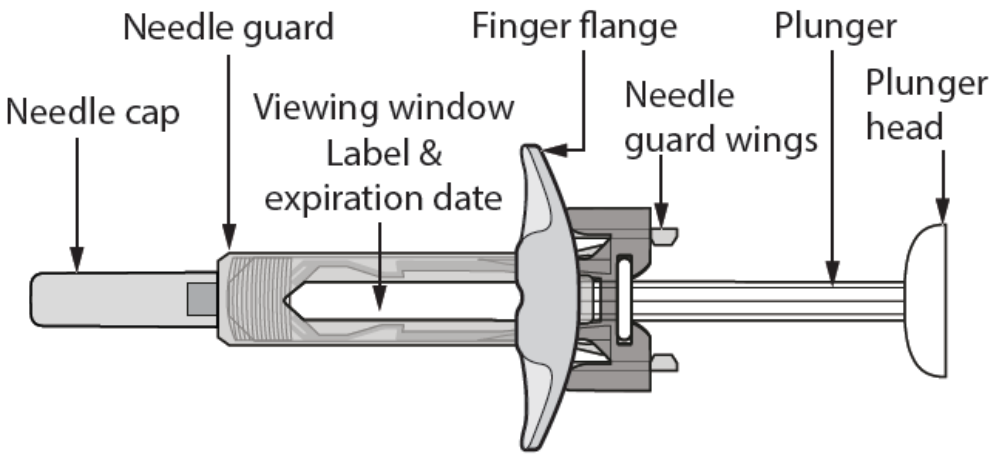


Figure A ERELZI prefilled syringe with needle guard and finger flange

- **In this configuration the Needle Guard is Activated- Do not use the pre-filled syringe (see Figure B)**

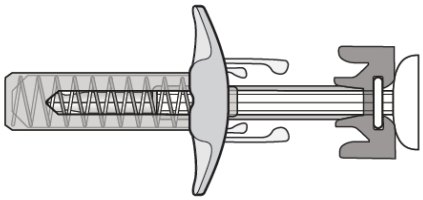


Figure B Device Activated – Do Not Use

- **In this configuration the Needle Guard is not activated and the prefilled syringe is ready for use (see Figure C)**

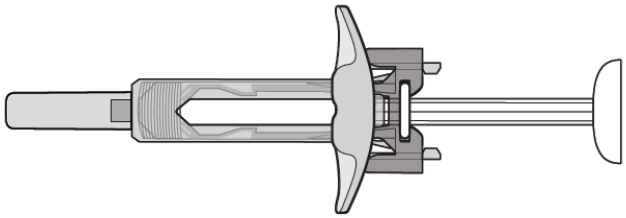


Figure C Device Ready to Be Used

What you need for your injection:

Included in the carton:

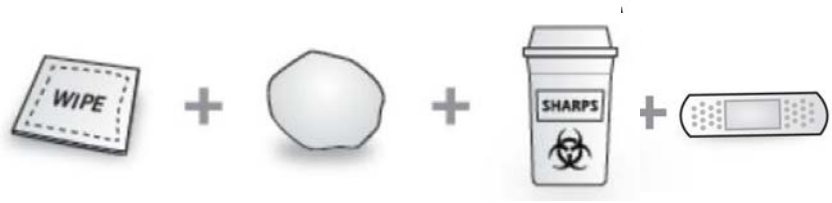
A new ERELZI prefilled syringe (**see Figure C**)

Each prefilled syringe contains 25 mg/0.5 mL or 50 mg/mL of ERELZI.

Not included in the carton (**see Figure D**):

Figure D

- 1 Alcohol wipe
- 1 Cotton ball or gauze
- Sharps disposal container
- 1 Adhesive bandage



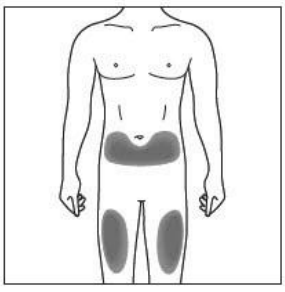
See **"How should I dispose of used ERELZI prefilled syringes?"** at the end of this Instructions for Use.

Step 1: Preparing the ERELZI Prefilled Syringe

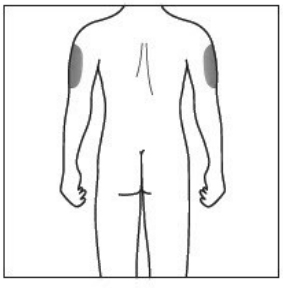
1. Find a clean, well-lit, flat work surface, such as a table.
2. Take the blister containing the ERELZI prefilled syringe out of the refrigerator and leave it **unopened** on your work surface for about 15 to 30 minutes to allow it to reach room temperature. **Do not** try to warm the ERELZI prefilled syringe by using a heat source such as hot water or a microwave.
3. Wash your hands well with soap and water.
4. Take the ERELZI prefilled syringe out of the blister.
5. Look through the viewing window. The liquid should be clear and colorless to slightly yellow. It is normal to see small white particles in the liquid. **Do not use** if the liquid is cloudy, discolored, or has large lumps, flakes, or particles in it. Return the prefilled syringe and the package it came in to your pharmacy.
6. **Do not** use the ERELZI prefilled syringe if it is broken or the needle guard is activated. Return the prefilled syringe and the package it came in to your pharmacy.
7. **Do not** use the ERELZI prefilled syringe if the expiration date has passed. Return the prefilled syringe and the package it came in to your pharmacy.

Step 2: Choosing and Preparing an Injection Site

Figure E



1. The recommended site is the front of your thighs. You may also use the lower abdomen, but **not** the area 2 inches (5 cm) around your navel (belly button) (**see Figure E**).
2. Choose a different site each time you give yourself an injection.
3. **Do not** inject into areas where the skin is tender, bruised, red or hard. Avoid areas with scars or stretch marks.
4. If you have psoriasis, **do not** inject directly into any raised, thick, red, or scaly sk
5. If a **caregiver** or **healthcare provider** is giving you your injection, they may also inject into your outer upper arm (**see Figure F**).



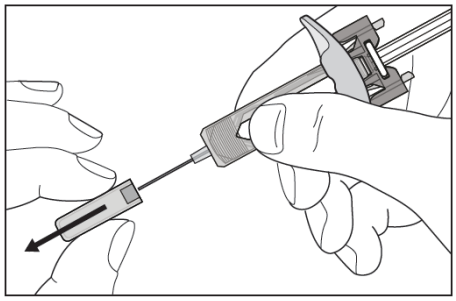
6. Using a circular motion, clean the injection site with the alcohol wipe. Leave it to dry before injecting. Do not touch the cleaned area again before injecting.

Step 3: Injecting ERELZI Using a Prefilled Syringe

Only remove the needle cap when you are ready to use the ERELZI prefilled syringe.

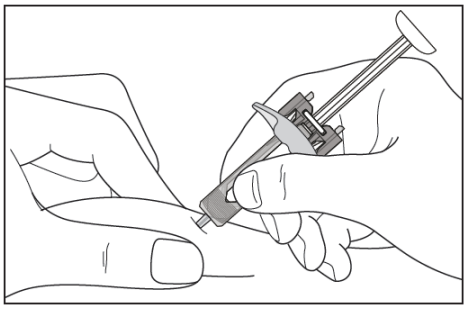
1. Carefully remove the needle cap from the ERELZI prefilled syringe (**see Figure G**). Throw away the needle cap. You may see a drop of liquid at the end of the needle. This is normal.

Figure G



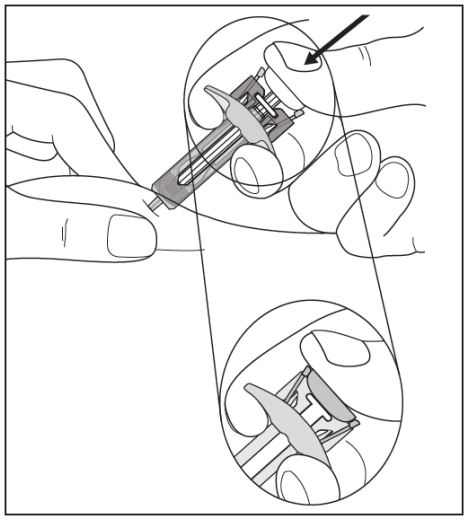
2. With one hand gently pinch the skin at the injection site. With your other hand insert the needle into your skin as shown (**see Figure H**). Push the needle all the way in to make sure that you inject your full dose.

Figure H



3. Hold the ERELZI prefilled syringe as shown (**see Figure I**). Slowly press down on the plunger as far as it will go, so that the plunger head is completely between the needle guard wings.

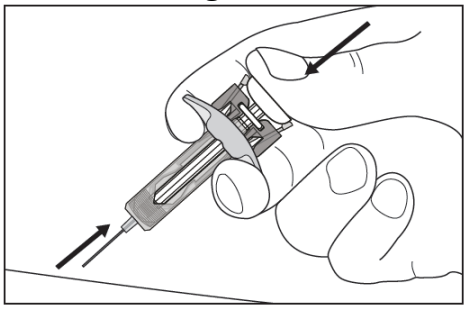
Figure I



4. Keep the plunger fully pressed down while you hold the syringe in place for 5 seconds.

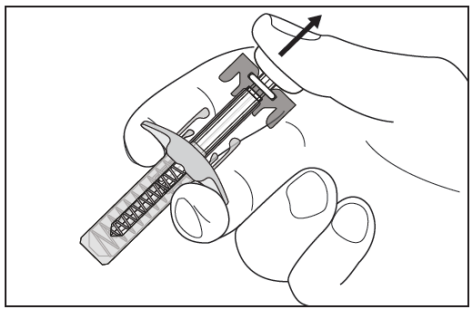
5. Keep the plunger fully pressed down while you carefully pull the needle straight out from the injection site **(see Figure J).**

Figure J



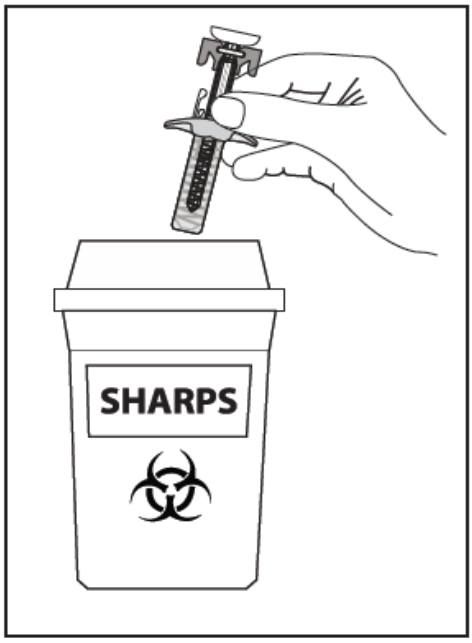
6. Slowly release the plunger and allow the needle guard to automatically cover the exposed needle **(see Figure K).**
7. There may be a small amount of blood at the injection site. You can press a cotton ball or gauze over the injection site and hold it for 10 seconds. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if needed.

Figure K



How should I throw away used ERELZI prefilled syringes?

Figure L



Put your used prefilled syringes in an FDA-cleared sharps disposal container right away after use **(see Figure L). Do not throw away (dispose of)** ERELZI prefilled syringes in your household trash.

If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles, syringes, and prefilled syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal

Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:

Sandoz Inc.

Princeton, NJ 08540

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At:

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