The safety information included in this document, unless otherwise noted, is from the worldwide ENBREL® safety database, including patients who have received ENBREL® in clinical trials since 1993 and 4 years of commercial experience with ENBREL® through November 2, 2002.

2.0 ENBREL® Experience

ENBREL® has been the subject of extensive investigation and safety evaluations since 1991, starting with cell culture toxicity studies, animal tolerability studies, through studies evaluating safety in normal human volunteers and patients with a variety of different medical conditions.

2.1 Clinical Trials in Patients with Rheumatic Diseases

The ENBREL® clinical trial database through 2002 includes 3389 patients who have received ENBREL® in Amgen- and Wyeth-sponsored rheumatic disease clinical trials for currently approved indications. In open-label extension studies, the efficacy and the safety profile associated with longer-term administration of ENBREL® (up to 6 years) remain stable over time. The following table reflects worldwide trial experience estimated through December 2002.

Table 2-1. Clinical Trial Experience Worldwide

	Patients (n)	Patient-years
North America	2119	5444
Ex-North America	1270	2892
Total	3389	8336

2.2 Post-Marketing Commercial Experience

The post-marketing worldwide commercial experience with ENBREL® through December 2002 includes greater than 150,000 patients treated, representing over 230,000 patient-years of therapy, depicted in Figure 2-1 below. The numbers of patients treated have recently increased substantially with the approval of the new ENBREL® manufacturing facility in Rhode Island.

7. Lymphoma Observations from Pharmacovigilance

7.1 Clinical Trial Observations

Lymphoma reports from clinical trials with ENBREL® will be represented by the standardized incidence ratio (SIR, the ratio of observed to expected cases). All "expected" numbers were calculated using the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database (11 Registries, 1992-99) using age, gender, and race-specific rates to predict the number of cases within the cohort of patients in clinical trials. Note that these expected numbers represent expectations for the United States general population and do not account for potential variations in rates that may exist among patients in diverse geographical regions, nor do they account for the increased risk known to exist in the RA population as described in Section 6.0. The confidence intervals were calculated under the assumption of a Poisson distribution for the observed cases (Breslow et al, 1987). The following data represent worldwide Amgen and Wyeth rheumatoid arthritis, juvenile rheumatoid arthritis, and psoriatic arthritis clinical studies performed with ENBREL®. The vast majority of the clinical experience is from rheumatoid arthritis clinical trials.

The only precise representation of lymphoma incidence can be determined in clinical trials as there is complete accounting for observed cases in the numerator, and total patient-year experience in the denominator is accurately available. The expected number of cases takes into consideration the age, gender, and race distribution of the treated population. In calculating the SIR, the numerator (observed cases) includes all cases observed during ENBREL® clinical trial experience (including 30 days after discontinuation of study drug) through December 31, 2002. The denominator (expected cases) is calculated from an estimation of the total experience in ENBREL® clinical trials to the end of December 2002 (representing 8336 patient-years of therapy, Table 7-1).

Table 7-1. SIR for Lymphoma Cases in ENBREL® Clinical Trials

Number of Cases	Expected*	SIR	95 % Confidence Intervals
6	2.59	2.31	0.85-5.03

*Expected in the US general population and does not account for increased risk in RA patients.

Three additional cases of lymphoma have been reported in patients previously exposed to ENBREL® in clinical trials, but the events occurred beyond 30 days after discontinuation of