
Information for the Arthritis Advisory Committee

04 March 2003

REMICADE[®] (infliximab)

Efficacy and Safety Review

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable laws and regulations. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you which is indicated as privileged or confidential.

Table of Contents	Page
Tables	5
Figures	6
Abbreviations	7
1.0 Introduction.....	8
2.0 REMICADE Patient Exposure.....	10
2.1 Clinical Trial Database.....	10
2.2 Postmarketing Exposure.....	10
3.0 Approved Indications and Efficacy Profile.....	11
3.1 Crohn's Disease.....	11
3.2 Rheumatoid Arthritis	12
4.0 Specific Safety Issues.....	13
4.1 Lymphoproliferative Diseases.....	13
4.1.1 Background	13
4.1.1.1 Lymphoproliferative Disease Incidence in the United States	13
4.1.1.2 The Impact of Rheumatoid Arthritis and Crohn's Disease on the Incidence of Lymphoproliferative Disease	14
4.1.1.2.1 Rheumatoid Arthritis.....	14
4.1.1.2.2 Crohn's Disease	15
Background Summary.....	16
4.1.2 Lymphoproliferative Disease in Clinical Trial Experience.....	16
4.1.2.1 Incidence of Lymphoproliferative Disease in Clinical Trials with Remicade	17
4.1.2.2 Lymphoproliferative Disease Incidence in Rheumatoid Arthritis Subpopulations of Patients in Clinical Trials.....	20
4.1.2.3 Characteristics of DMARD- and MTX-Resistant Patients Enrolled in Remicade Clinical Trials	20
4.1.2.4 Lymphoproliferative Disease Risk Modifiers in the Patients Who Developed Lymphoma.....	22
4.1.2.5 Characteristics of Lymphomas that Developed in Patients Enrolled in Remicade Clinical Trials	23
4.1.2.6 Clinical Course of Patients Who Developed Lymphoproliferative Disease During Clinical Trials of Remicade or During Long-term Safety Follow-up.....	25
4.1.3 Registries.....	27
4.1.3.1 National Database Registry of Rheumatoid Arthritis.....	27

	4.1.3.2	The Therapy Resource Evaluation and Assessment Tool (TREAT™) Registry of Crohn's Disease.....	28
4.1.4		Postmarketing Reports	30
	4.1.4.1	Distribution of Lymphoma Reports by Indication....	30
	4.1.4.2	Latency.....	31
	4.1.4.3	Other Suspect Drugs and Concomitant Medications Analysis.....	32
4.1.5		Discussion.....	33
	4.1.5.1	Comparison of the Effect of Different TNFα Blockers on LPD Incidence.....	35
4.2		Non-Lymphoproliferative Malignancies/Solid Tumors.....	37
	4.2.1	Clinical Trial Data.....	37
	4.2.2	Postmarketing Data	43
	4.2.2.1	Overview	43
	4.2.2.2	Cases Received Cumulatively, 24 August 1998 through 23 February 2002.....	43
	4.2.2.2.1	Distribution of Malignancies	43
	4.2.2.2.2	Latency.....	44
	4.2.3	Labeling.....	46
	4.2.3.1	Precautions Section.....	46
	4.2.3.2	Adverse Reactions Section.....	46
	4.2.4	Discussion and Conclusions.....	46
4.3		Tuberculosis and Opportunistic Infections	47
	4.3.1	Tuberculosis	47
	4.3.1.1	Clinical Trial Data.....	47
	4.3.1.2	Postmarketing Data	47
	4.3.1.2.1	Cumulative Surveillance (23 August 1998 through 23 August 2002)	47
	4.3.1.2.1.1	Tuberculosis Reports in the United States.....	47
	4.3.1.2.1.2	Tuberculosis Education Program.....	49
	4.3.1.2.1.3	Tuberculosis Cases Outside of the United States	50
	4.3.1.3	Labeling.....	51
	4.3.1.3.1	Bolded Warnings Section:.....	51
4.3.2		Opportunistic Infections	52
	4.3.2.1	Clinical Trial Data.....	52
	4.3.2.2	Postmarketing Data	52
	4.3.2.2.1	Overview.....	52
	4.3.2.2.2	Surveillance (23 February 2002 through 23 August 2002).....	52
	4.3.2.3	Labeling.....	54
	4.3.2.4	Discussion.....	54
4.3.3		Overall Conclusions	54

4.4	Neurological Events	55
4.4.1	Demyelinating Disorders.....	55
4.4.1.1	Clinical Trial Data.....	55
4.4.1.2	Postmarketing Data	55
4.4.1.2.1	Results.....	55
4.4.1.2.1.1	Central Demyelination.....	55
4.4.1.3	Labeling.....	56
4.4.1.3.1	Warnings Section.....	56
4.4.1.3.2	Labeling Supplement	56
4.4.1.4	Discussion.....	56
4.4.2	Optic Neuritis	57
4.4.2.1	Clinical Trial Data.....	57
4.4.2.2	Postmarketing Data	57
4.4.2.2.1	Cumulative Experience (23 August 1998 through 23 August 2002)	57
4.4.2.3	Labeling.....	58
4.4.2.4	Discussion.....	58
4.4.2.4.1	Conclusions	58
4.5	Congestive Heart Failure.....	59
4.5.1	Clinical Trial Data.....	59
4.5.2	Labeling.....	60
4.5.2.1.1	CONTRAINDICATIONS	60
4.5.2.1.2	Warnings Section:.....	60
4.5.2.1.3	Adverse Reactions:.....	60
5.0	Summary and Conclusions.....	62
5.1	Benefits/Risks.....	62
5.1.1	Benefits.....	62
5.1.2	Risk.....	63
5.2	Conclusions	64
6.0	Bibliography.....	66
Appendix A	Calculation of Standard Incidence Ratios	69
Appendix B	Listing of Lymphomas Reported Cumulatively by Indication and Adverse Event Term.....	70

Tables

Table 1	Increased lymphoproliferative disease risk in patients with RA.....	14
Table 2	Disease characteristics associated with increased risk for lymphoma [Baecklund, 1998]	15
Table 3	Increased lymphoproliferative disease risk in patients with CD.....	16
Table 4	Number of lymphomas observed in Remicade-treated and placebo treated subjects with RA and CD compared to the incidence rates for age, gender, and race-matched individuals in the general US population; 1999 SEER.....	18
Table 5	Demographics and disease characteristics of ATTRACT patients and four RA patients who developed lymphoma.....	21
Table 6	Disease duration and history of exposure to immunosuppressive agents in patients who developed lymphoma in clinical trials	22
Table 7	Remicade exposure and lymphoma histology and latency in patients who developed lymphoma in clinical trials	24
Table 8	Lymphoma rates in patients enrolled in the National Database of Rheumatoid Arthritis	28
Table 9	Demographic summary of patients in the TREAT Registry.....	29
Table 10	Lymphomas in patients with CD enrolled in the TREAT Registry.....	30
Table 11	Distribution of lymphomas by type and indication.....	31
Table 12	Latency (days) since first exposure by indication.....	32
Table 13	Other suspect drugs and concomitant medication by indication.....	33
Table 14	Summary of subjects with 1 or more non- lymphoproliferative disease malignancies who participated in Centocor-sponsored Remicade clinical studies ^a	39
Table 15	Number of observed and expected non-lymphoma malignancies ^a in Remicade treated subjects; 1999 SEER, adjusted for age, gender and race	41
Table 16	Number of observed and expected non-lymphoma malignancies ^a in placebo treated subjects; 1999 SEER, adjusted for age, gender and race	42
Table 17	Cumulative non- lymphoproliferative disease malignancy by indication.....	44
Table 18	Latency (days) since first exposure by indication, cumulative experience.....	45
Table 19	Exposure data for cumulative tuberculosis reports by region.....	49
Table 20	Potentially opportunistic infections.....	53
Table 21	Postmarketing surveillance data for neuropathic conditions.....	55
Table 22	Demographics of cumulative reports: optic neuritis	57

Figures

Figure 1	Cumulative tuberculosis cases: United States (24 August 1998-23 August 2002)	50
----------	--	----

Abbreviations

ACCENT	A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen I
ATTRACT	Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy
BLA	Biologics License Application
CD	Crohn's disease
CHF	congestive heart failure
CIPD	chronic inflammatory demyelinating polyradiculoneuropathy
EU	European Union
FDA	Food and Drug Administration
GBS	Guillain-Barre Syndrome
GI	gastrointestinal
IV	intravenous
LPD	lymphoproliferative disease
MTX	methotrexate
NEC	not elsewhere classified
NOS	not otherwise specified
NYHA	New York Heart Association
OI	opportunistic infection
PK	pharmacokinetics
PO	by mouth (per os)
PROMPT	Profiling Remicade® Onset with Methotrexate in a Prospective Trial
PSUR	Periodic Safety Update Report
RA	rheumatoid arthritis
SEER	Surveillance Epidemiology and End Results
SIR	standardized incidence rate (ratio)
TB	tuberculosis
TNF	tumor necrosis factor
US	United States
WHOART	World Health Organization Adverse Reaction Terms

1.0 Introduction

Remicade® (infliximab) is a monoclonal antibody that binds with high affinity and specificity to human tumor necrosis factor alpha (TNF α) and neutralizes its biologic activity. Clinical trials have demonstrated the efficacy of Remicade in the treatment of both rheumatoid arthritis (RA) and Crohn's disease (CD). Remicade was approved in the United States (US) for the short-term treatment of CD in August 1998; for the treatment of signs and symptoms of RA in November 1999; for the inhibition of structural damage due to RA in December 2000; and for the improvement in physical function in RA in February 2002. Remicade is the first and only anti-rheumatic drug or biologic approved for this indication based on the assessment in physical function and disability in patients with rheumatoid arthritis.

In June 2002, Remicade received Food and Drug Administration (FDA) approval for inducing and maintaining clinical remission in patients with moderately-to-severe Crohn's disease. A supplemental Biologics License Application (sBLA) for maintenance therapy in patients with fistulizing Crohn's disease is currently under review and received priority status from the FDA. To date, Remicade is the only anti-TNF agent approved for the treatment of Crohn's disease.

Although the benefit/risk profile of Remicade favors a strong benefit (as summarized in Section 5.0), some serious risks have been identified via postmarketing reports such as, serious infections, including opportunistic infections and tuberculosis (TB). During August and September 2001, Centocor launched a TB education program in the US. The follow-up study of the education program indicated that the education program was successful in having physicians perform screening tests for latent TB and to initiate anti-TB therapy, when necessary, before initiating Remicade. Importantly, this effort led to a continuous decline in the number of spontaneous reports of active TB in the US over the past year.

Currently, Centocor continues to fortify its communication plans regarding the risk of TB with health care providers as well as patients. In addition, Centocor has ongoing clinical trials and patient registries to collect data on known and potential risks with Remicade administration. Finally, Centocor continues to collect long-term safety data on Remicade-treated patients to better understand these potential risks, such as lymphoproliferative disease (LPD) and malignancies.

This briefing document will provide an overview of the efficacy and safety profile of Remicade to facilitate the Arthritis Advisory Committee's discussion on the potential safety risks of anti-TNF agents and steps that may reduce these risks.

A summary of the efficacy of Remicade for labeled indications and a summary of selected adverse events of special interest is provided, including LPD, non-LPD malignancies, TB, opportunistic infections, neurological disorders (demyelinating disorders and optic neuritis), and congestive heart failure (CHF). The information was

obtained from the Integrated Summary of Safety for Remicade of August 9, 2002 and from the Sixth Periodic Safety Update Report (PSUR 6) of October 17, 2002. In addition, updated information from ongoing clinical trials has been submitted to the Food and Drug Administration (FDA). All available information on the occurrence of lymphoma and malignancies in completed Centocor-sponsored clinical trials is included in this assessment. In addition, preliminary data from a large placebo-controlled Phase III trial (ASPIRE) in over 1,000 patients with rheumatoid arthritis are included in order to evaluate the potential risk of lymphoma and malignancies in an early RA patient cohort.

2.0 REMICADE Patient Exposure

2.1 Clinical Trial Database

To date, the efficacy and safety of Remicade has been assessed in 15 completed clinical trials, as well as a number of recently completed, ongoing or partner-sponsored studies. Of these 15 completed trials, 1,678 patients have received Remicade, comprising over 3,445 patient-years of experience.

Since Remicade received FDA approval for the rheumatoid arthritis indication, two additional large Phase III clinical trials are ongoing: ASPIRE and START, comprising over 2,000 patients with approximately 1,700 patients with rheumatoid arthritis who have received long-term Remicade therapy.

2.2 Postmarketing Exposure

As of August 23, 2002, an estimated 365,000 patients worldwide (233,000 patients in the United States and 132,000 patients outside the US) have been treated with commercial Remicade, representing more than 554,000 patient-years of exposure. Of the 365,000 patients who have received Remicade, 198,000 have received it for RA, 157,000 for CD, and 10,000 for other conditions.

In addition, between September 2002 to end of year of 2002, an estimated additional 56,000 patients have received Remicade. In total, since its approval in August 1998, more than 400,000 patients have been treated with Remicade, with approximately 750,000 patient-years of exposure.

3.0 Approved Indications and Efficacy Profile

3.1 Crohn's Disease

Remicade is indicated for reducing signs and symptoms of moderately-to-severely active CD in patients who have had an inadequate response to conventional therapy. It is also indicated for reducing the number of draining enterocutaneous fistulas in patients with fistulizing CD (FDA approved 1998), and for inducing and maintaining clinical remission in this patient population (marketing approval from FDA granted 2002). Approval from the FDA is pending for the use of Remicade in maintaining fistula closure in patients with fistulizing CD (sBLA priority review granted January 2003).

The initial FDA approval for the treatment of CD was based upon the results of two open-label trials (C0168T08 and C0168T11) and two randomized, placebo-controlled trials (C0168T16 and C0168T20). The effectiveness of Remicade in the treatment of CD has been evaluated in a total of seven completed clinical trials including two open-label studies and four double-blind placebo-controlled clinical trials. Below is a summary of ACCENT I and ACCENT II, two large, multi-center, double-blind, placebo-controlled clinical trials of Remicade for the treatment of CD.

ACCENT I

The study, titled, *A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen I* (ACCENT I) demonstrated that maintenance Remicade therapy prolonged response and remission compared with a single dose of Remicade in patients with moderate-to-severe CD. Five hundred seventy-three patients in this large randomized study were treated with Remicade maintenance regimens of 5 or 10 mg/kg administered every 8 weeks for up to 54 weeks. The study had two primary endpoints: the proportion of patients in clinical remission at week 30, and the time to loss of clinical response at week 54. All analyses were based on patients who were considered to be responders at the 2-week time point. ACCENT I demonstrated that patients who responded to an initial dose of Remicade and received Remicade maintenance treatment every 8 weeks were more likely to be in remission at weeks 30 and 54, to discontinue corticosteroids, and to maintain a longer clinical response than those treated with a single dose of Remicade (Hanauer, et al, 2002). In 2002, the FDA approved the use of Remicade for inducing and maintaining clinical remission in patients with moderately-to-severely active CD who have had an inadequate response to conventional therapy based on the results of the 54-week data from the ACCENT I trial.

ACCENT II

ACCENT II was a large, placebo-controlled, randomized trial in which all 306 patients who had fistulizing CD received a 3-dose induction of Remicade 5 mg/kg, and were then assessed for response, subsequent to receiving either placebo or Remicade 5 mg/kg every

8 weeks. The primary objective of the study was to determine the efficacy and safety of a 3-dose induction of Remicade followed by either Remicade or placebo maintenance in reducing the number of draining fistulas. A major secondary objective was to evaluate the ability of Remicade to induce complete fistula response (absence of draining fistulas). The final results of the study demonstrated the efficacy of Remicade induction and maintenance therapy in reducing the number of draining fistulas and achieving a complete fistula response. The results of the study have been submitted to the FDA as an sBLA. In early January 2003, the FDA granted a priority review of the submission.

3.2 Rheumatoid Arthritis

Remicade in combination with methotrexate (MTX) is also approved for reducing the signs and symptoms (FDA approved 1999), inhibiting radiographic progression (FDA approved 2000), and improving physical function in patients with RA who have had an inadequate response to MTX (FDA approved 2002).

The effectiveness of Remicade in the treatment of RA was evaluated in four completed, randomized, double-blind, placebo-controlled trials. The largest pivotal study is summarized briefly below.

ATTRACT

The ATTRACT trial (also titled *Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy*; Maini et al, 1999; Lipsky et al, 2000) was a large placebo-controlled trial of 428 patients treated with Remicade regimens of at least 3 mg/kg administered every 8 weeks for up to 102 weeks. Results from ATTRACT show that significantly more patients treated with Remicade plus MTX had 20, 50, and 70 % responses in disease signs and symptoms (as determined by The American College of Rheumatology [ACR] index) than did patients who received MTX plus placebo. The clinical benefits of Remicade were evident at almost all time points including after 30, 54, and 102 weeks of therapy. Remicade in combination with MTX was approved by the FDA for reducing disease signs and symptoms, inhibiting the progression of radiographic damage, and improving physical function in patients with moderately-to-severely active RA who have had an inadequate response to MTX. All key analyses of the 102-week data from ATTRACT were supportive of previous results from the 30-week and 54-week analyses and demonstrated that the responses observed as early as 2 weeks after the first infusion could be maintained through 2 years.

4.0 Specific Safety Issues

4.1 Lymphoproliferative Disease

There are several recent reports of the development of lymphoproliferative disease (LPD) in patients using TNF α blocking agents. These observations have again raised questions about the possible association of these agents on a patient's risk of developing LPD (Brown, 2002). It is clear that more data are needed to better characterize the risk of LPD in patients receiving anti-TNF therapy and to allow a comprehensive assessment of the overall risk/benefit for these therapies. To this end, a number of different datasets are included in this assessment:

- Background information on the incidence of LPD in the US population and the effect of RA and CD on the incidence of LPD is summarized in Section 4.1.1.
- More detailed information on the occurrence of LPD in Remicade-treated patients is analyzed from three different data sources:
 - clinical trials experience (section 4.1.2)
 - experience in RA and CD disease registries (Section 4.1.3)
 - experience in postmarketing pharmacovigilance (Section 4.1.4)
- Possible interpretations and implications of these data are discussed (Section 4.1.5).

4.1.1 Background

4.1.1.1 Lymphoproliferative Disease Incidence in the United States

Lymphoproliferative diseases comprise a large family of malignancies that are all lymphoid-derived but are diverse with regard to their pathophysiology, natural history, and treatment. Lymphoproliferative diseases account for approximately 5% of all new cancer diagnoses each year in the U.S.; more than 60,000 new cases of LPD are diagnosed annually. Over a lifetime, the current risk of developing LPD is just over 2% in the U.S. Lymphoproliferative disorders are broadly divided into Hodgkin disease (HD) and non-Hodgkin lymphomas (NHL). Histopathologically, these diseases are distinct, with HD being characterized by the presence of Reed-Sternberg cells, which comprise part of the malignant cell population. The patterns of spread, natural history, and treatments of HD and the various diseases that comprise NHL are also distinct. The incidence of NHL has been increasing by approximately 3% per year for the past four decades, and more than 80% overall since 1973. The reasons for this increase are not completely understood, but a number of factors, including the increasing age of the US

population and the HIV epidemic are almost certainly related to this increase (for review, see DeVita, 2001 and Hoffman, 2000).

4.1.1.2 The Impact of Rheumatoid Arthritis and Crohn's Disease on the Incidence of Lymphoproliferative Disease

Remicade is indicated in patients with RA and CD. An understanding of the background incidence of LPD in these target populations irrespective of therapies is essential before determining if Remicade has an effect on the incidence of LPD.

4.1.1.2.1 Rheumatoid Arthritis

Risk of Lymphoproliferative Disease in Patients with Rheumatoid Arthritis

There are no prospective studies to determine the incidence of LPD in RA. Analysis of three large patient registries suggests that patients with RA have a significantly higher risk (approximately 2-3 fold) of developing LPD than the general population (Table 1). Though some smaller studies (of fewer than 1000 pts) have not consistently confirmed this elevated risk (Table 1), these studies are likely underpowered to detect the level of risk conferred by a history of RA.

Table 1 Increased lymphoproliferative disease risk in patients with RA

Study Origin	Ref.	N	NHL		HD	
			RR	95% CI	RR	95% CI
Finland, 1982	Isomaki, 1982	46101	2.7	1.9 - 3.7	2.8	1.7 - 4.4
Denmark, 1996	Mellemkjaer, 1996	20699	2.4	1.9 - 2.9	3.4	1.8 - 5.6
Sweden, 1993	Gridley, 1993	11683	1.9	1.3 - 2.6	2.3	1.2 - 4.1
Canada, 1997	Cibere, 1997	862	0.6	0.1 - 1.6	0	0 - 8.5
Japan, 1995	Moritomo, 1995	655	0.8 ^a	0.0 - 7.4 ^a	NC	NC
US, 1985	Katusic, 1985	521	1.2	0.2 - 3.4	NC	NC
England, 1985	Prior, 1985	489	24.1	p < 0.05	12.5	p < 0.001

^a All hematopoietic disorders.

HD = Hodgkin's disease

NC = not calculated

NHL = non-Hodgkin's lymphomas

RR = observed relative risk compared with the general population

95% CI = 95% confidence interval

Impact of Rheumatoid Arthritis Disease Characteristics on Lymphoproliferative Disease Incidence

Among patients with RA, certain disease characteristics have been associated with a higher risk of LPD. Analyses of RA patients that develop LPD show that, compared with RA patients in general, they are usually older, have long disease duration and a high cumulative methotrexate exposure (Sibilia, 1998; Symmons DP, 1984; Symmons DP 1988; Jones, M, 1996). Additionally, epidemiological analysis show that several other factors, including a high level of inflammatory activity, poor functional class (class III or IV), involvement of both small and large joints, and extra-articular disease manifestations are associated with higher odds ratios for LPD development (Table 2 [Baecklund, 1998]).

Table 2 Disease characteristics associated with increased risk for lymphoma [Baecklund, 1998]

	Odds Ratio	95% CI
Inflammatory activity		
Low	1.0	
Medium	5.4	0.7 - 42.0
High	25.8	3.1 – 213.0
Functional class		
I	1.0	
II	1.1	0.2 - 5.9
III	4.7	0.8 - 26.2
IV	12.9	2.1 - 76.8
Joints affected		
Small	1.0	
Small and large	9.3	2.1 - 41.5
Other characteristics		
Complications/extra-articular manifestations	2.1	0.9 - 4.9
Atlantoaxial subluxation	11.2	1.2 – 100.0
Amyloidosis	9.0	0.9 - 86.5
Nodules	7.6	1.5 - 37.1

4.1.1.2.2 Crohn's Disease

Risk of Lymphoproliferative Disease in Patients with Crohn's Disease

Crohn's disease has also been reported to be associated with an increased risk of lymphoma, though some controversy still exists concerning the strength and magnitude of this association. The lower prevalence of CD compared with RA has made the systematic study of the association of CD with LPD more problematic. Therefore, fewer studies have been performed in CD, and these studies also tend to be smaller, leading to more uncertainty about the association of CD and LPD. Table 3 presents published

information on the relative risk of LPD in CD patients compared with the general population.

Table 3 Increased lymphoproliferative disease risk in patients with CD

Study Origin	Ref.	N	NHL	
			RR	95% CI
US, 1985	Greenstein, 1985	1227	4.7	p < 0.05
Canada, 2001	Bernstein, 2001	2857	2.4	1.2 – 5.0
Sweden, 1991	Ekbom, 1991	1655	0.4	0 - 2.4
Denmark, 2000	Mellemkjaer, 2000	2645	1.5	0.4 – 3.7
England, 2001	Lewis, 2001	6605	1.4	0.5 – 3.4

NHL = non-Hodgkin's lymphomas

RR = observed relative risk compared with the general population

Impact of Crohn's Disease Characteristics on Lymphoproliferative Disease Incidence

It is reasonable to predict that LPD incidence might vary as a function of disease duration and severity in CD, but the relationship of disease characteristics has not been studied in patients with CD.

Background Summary

Combined, available studies in the medical literature indicate that the baseline risk of LPD in patients with RA and CD is higher than the general population. Moreover, for RA in particular, certain risk factors such as age, disease duration, history of exposure to conventional immunosuppressive drugs, burden of disease, and degree of inflammation may be predictive of the magnitude of LPD risk, and therefore, may allow identification of the subpopulations of patients most at risk of developing LPD.

4.1.2 Lymphoproliferative Disease in Clinical Trial Experience

Information presented in this section summarizes (i) data collected in Centocor-sponsored Remicade clinical trials reported in the Integrated Summary of Safety provided with the ACCENT II sBLA and (ii) data from the ASPIRE trial of Remicade in patients with MTX-naïve, early RA. Data from ASPIRE includes preliminary results from a blinded, unlocked database. Therefore, counts of patients and number of patients-years assigned to Remicade or placebo were based on the ratio of patients as planned according to the study design. All lymphomas observed in ASPIRE (N=0) were counted as if they occurred in Remicade-treated patients (worse case analysis).

4.1.2.1 Incidence of Lymphoproliferative Disease in Clinical Trials with Remicade

In total, 2,421 patients have been exposed to Remicade in clinical trials: 1,106 patients with CD and 1,298 patients with RA. Three patients developed LPD while enrolled in clinical trials, two with CD and one with RA. Three additional patients developed LPD during long-term safety follow up; all three patients had RA. The incidence of LPD in clinical trials has been calculated for patients exposed to Remicade and placebo (Table 4). Standardized incidence ratios (SIRs) compare lymphoma incidence in these patients to rates observed in the general US population. It is important to underscore that these SIRs do not compare the incidence of lymphoma in patients who participated in clinical trials to that of a comparable RA and CD population.

Table 4 Number of lymphomas observed in Remicade-treated and placebo treated subjects with RA and CD compared to the incidence rates for age, gender, and race-matched individuals in the general US population; 1999 SEER

Population	N	Total Subject- yrs Follow-up	Median Subject- yrs Follow-up	Observed Number of Lymphoma Cases	Number of Lymphoma Cases Expected in Age- matched Individuals in the General US Population ^a	SIR	SIR 95% CI ^b
<u>Remicade</u>							
All studies ^c	2421	4147.8	1.00	6	0.86	6.98	[2.56, 15.19]
All rheumatoid arthritis studies	1298	2458.4	0.80	4	0.63	6.35	[1.73, 16.26]
MTX-naïve, early RA study ^d	743	702.6	0.78	0	0.17	0.00	[0, 21.48]
DMARD resistant rheumatoid arthritis studies	555	1755.8	3.30	4	0.45	8.89	[2.42, 22.76]
Crohn's disease studies	1106	1646.2	1.37	2	0.23	8.70	[1.05, 31.41]
<u>Placebo</u>							
All studies ^c	489	691.3	0.32	0	0.15	0.00	NC ^e
All rheumatoid arthritis studies	430	589.5	0.32	0	0.14	0.00	NC ^e
MTX-naïve, early RA study ^d	297	279.5	0.31	0	0.07	0.00	[0, 52.18]
DMARD resistant rheumatoid arthritis studies	133	309.9	3.00	0	0.07	0.00	NC ^e
Crohn's disease studies	56	94.8	2.45	0	0.01	0.00	NC ^e

March 4, 2003

FDA Arthritis Advisory Committee Briefing Document

Table 4 **Number of lymphomas observed in Remicade-treated and placebo treated subjects with RA and CD compared to the incidence rates for age, gender, and race-matched individuals in the general US population; 1999 SEER (continued)**

^a The expected number of subjects with malignancies is based on the SEER Database (1999), adjusted for age, gender, and race.

^b Upper confidence limit was calculated based on Byar Approximation provided in the formula 8.1 and 8.2 given in the reference Sahai and Khurshid (1993).

^c Twenty patients enrolled in clinical studies were treated for indications other than RA and CD.

^d ASPIRE: A) Preliminary results from blinded, unlocked database; B) Counts of subjects and number of subject years of follow-up assigned to Remicade or placebo based on the ratio of subjects as planned according to the study design;

^e NC – Not calculated

SEER = Surveillance Epidemiology and End Results

SIR = standardized incidence rate (ratio)

4.1.2.2 Lymphoproliferative Disease Incidence in Rheumatoid Arthritis Subpopulations of Patients in Clinical Trials

That the incidence of LPD was higher in patients enrolled in Remicade clinical trials compared with the general US population supports previous evidence that the risk of LPD is increased by RA and CD (see Section 4.1.1.1). However, RA and CD are reported to confer only a 2 to 3 fold increased relative LPD risk compared to the general US population. The overall SIR of 6.98, as well as the SIR in RA patients (6.35) and the SIR in CD patients (8.70), suggests that LPD risk was higher in Remicade-treated patients than in the general RA and CD patient populations. In RA, patient characteristics associated with more aggressive or longstanding disease have been shown to increase the risk of LPD (Section 4.1.1.2.1). To determine if these characteristics might effect the SIR in patients treated with Remicade in clinical trials, LPD incidence in patients who are MTX-naïve, early RA (patients enrolled in the ASPIRE trial of Remicade in early RA) was compared with the LPD incidence in patients with DMARD- and MTX-resistant, high inflammatory burden disease (patients enrolled in all other RA trials). Not surprisingly, the SIR value was lower in patients with early RA (SIR=0.00) compared with patients who were DMARD- and MTX-resistant (SIR=8.89; Table 4). The results of preliminary data from ASPIRE suggest that risk factors associated with DMARD- and MTX-resistant RA increase the risk of LPD. Because no data are available on patients with less severe CD, similar comparisons were not possible in CD clinical trials.

4.1.2.3 Characteristics of DMARD- and MTX-Resistant Patients Enrolled in Remicade Clinical Trials

The high SIR for LPD in clinical trials of patients with DMARD- and MTX-resistant RA suggests that these patients may have a higher baseline risk of LPD. To examine this possibility, risk modifiers associated with LPD risk were examined in patients enrolled in the ATTRACT clinical trial, the population that constitutes the majority of DMARD- and MTX-resistant patients. As a group, these patients had disease characteristics that would be expected to raise their lymphoma risk (Table 2, [Baecklund, 1998]). Notably 48.6% of patients were in functional class III, which is associated with an unadjusted odds ratio of 4.7 compared with the general RA population (Baecklund, 1998). The high mean score on the Health Assessment Questionnaire (HAQ), the low Medical Outcomes Study Short-Form General Health Survey (SF-36) physical component scores, the high mean tender and swollen joint counts, erythrocyte sedimentation rates, and C-reactive protein levels suggest that the patient population studied, as a group, had high inflammatory activity, which is associated with an unadjusted odds ratio of 25.8 compared with the general RA population (Baecklund, 1998). These data show that a subpopulation of patients who have a high risk of LPD compared with the general RA population were enrolled in the ATTRACT clinical trials. The high SIR for LPD in these DMARD- and MTX-resistant RA patients is compatible with their baseline disease status.

The risk factors for LPD have not been characterized in patients with CD. Therefore, similar analyses in CD patients enrolled in clinical trials of Remicade could not be performed.

Table 5 Demographics and disease characteristics of ATTRACT patients and four RA patients who developed lymphoma

Characteristic	All Patients (ATTRACT)	Patient # T22-05012	Patient # T22-11010	Patient # T07-01020	Patient # T09-03006
Gender	78% Female	Female	Male	Male	Male
Race	91% White	Black	White	White	White
Age at entry	52 (mean)	74	71	48	60
Anatomical stage		IV	II	III	III
Stage I/II	38.8%				
Stage III	48.0%				
Stage IV	7.7%				
Functional class		III	II	II	II
Class I/II	46.0%				
Class III	48.6%				
Class IV	0.7%				
Disease duration (years)	10.4 ± 8.6	37	10	16	16
Rheumatoid factor	80.8% Positive	Positive	Positive	Positive	NA
Anti-nuclear antibodies	19.7% Positive	Positive (1:640)	Positive (1:320)	ND	ND
Tender/swollen joints	32/22	53/18	62/18	42/24	22/11
HAQ ^a	1.7 ± 0.6	2.0	2.6	ND	ND
SF-36 (physical component) ^b	26 ± 8	22.2	18.5	ND	ND
CRP (mg/dL)	3.8 ± 3.9	0.34	1.69	10.7	5.5
ESR (mm/hr)	50 ± 24	38	48	80	52

^a Scores can range from 0 (no difficulty) to 3 (unable to perform the activity)

^b Scores for the Medical Outcomes Study Short-Form General Health Survey (SF-36) were compared with normalized scores for the general US population, for which the mean score was 50±10. Higher scores indicate a better quality of life.

NA = not applicable

ND = not determined

4.1.2.4 Lymphoproliferative Disease Risk Modifiers in the Patients Who Developed Lymphoma

The risk factors for LPD were also examined in the patients who developed lymphomas (Table 5 and Table 6). Table 5 shows characteristics of the RA patients who developed lymphomas compared with that of the ATTRACT patient population. As noted above, the ATTRACT population had a large proportion of RA patients with a poor functional status, high inflammatory activity, and DMARD- and MTX-resistant disease. The mean age in the ATTRACT population as a whole was 52. Three of the four patients who developed lymphomas were over 60 (60, 71, and 74 years of age), and one patient was 48 years of age. Three of four patients had longer disease duration than the mean duration of RA in ATTRACT, and the two patients for whom HAQ and SF-36 scores were available were more debilitated by their disease than that indicated by the average HAQ and SF-36 scores in ATTRACT. The older age and high inflammatory activity of these patients is consistent with previous observations that these characteristics are risk modifiers of LPD in RA (Baecklund, 1998, Sibilia, 1998). The immunosuppressive agent exposure histories of some patients are not completely known. However, it is notable that both of the RA patients whose methotrexate exposure history could be quantified had been exposed to greater than 3,000 mg methotrexate cumulatively. Moreover, both of the patients with CD had extensive exposure to azathioprine (Table 6).

Table 6 Disease duration and history of exposure to immunosuppressive agents in patients who developed lymphoma in clinical trials

Disease Population	Pat. No.	Previous Meds	Disease Severity
RA	T22-05012	MTX x 15 yrs (> 3000 mg) prednisone	RA x 37 yrs
	T07-01020	Azathioprine, MTX, prednisone (cumulative exposures not known)	RA x 16 yrs
	T09-03006	MTX (cumulative exposure not known)	RA x 16 yrs
	T22-11010	MTX x 7 yrs (> 3000 mg) azathioprine, etanercept	RA x 10 yrs
CD	T16-08002	Azathioprine x 6 yrs	Crohn's disease x 29 yrs
	T21-32001	Azathioprine x 1 - 2 yrs prednisone > 2 yrs	Crohn's disease x 6 yrs

4.1.2.5 Characteristics of Lymphomas that Developed in Patients Enrolled in Remicade Clinical Trials

To evaluate a common pathogenesis among the lymphomas that developed in patients enrolled in clinical trials, a number of important parameters were assessed. These included: treatment with Remicade, the classification of the lymphoma, and latency of lymphoma development after treatment with Remicade (Table 7). No obvious commonalities were observed in any of these parameters, i.e., none of these parameters were found to be informative or predictive for the development of lymphoma. Importantly, no dominant histology was observed in the analyses. Rather, all six patients who developed lymphoma in the clinical studies had distinct histologic profiles, suggesting that distinct pathophysiologic mechanisms (and possibly initiating events) were associated with each event. Furthermore, only one of the five patients with non-Hodgkin lymphoma had a high-grade tumor, the grade most commonly seen among immunodeficiency-related lymphomas (e.g., post transplant LPD) and the grade that might, therefore, be anticipated to occur more commonly if there was a clearer association between the development of lymphoma and use of TNF-blocking therapies.

Table 7 Remicade exposure and lymphoma histology and latency in patients who developed lymphoma in clinical trials

Disease Population	Pat. No.	Gender	Race	Age at Entry	Cancer Type Lymphoma	Remicade Dose Initial	Remicade Dose Re-treatment	Time of Diagnosis	Latency
RA	T22-05012	F	Black	74	Large B-cell lymphoma	10 mg/kg	10 mg/kg q 4 wk	on-study	30 wks into ATTRACT Trial
	T07-01020	M	White	48	B-cell NHL; high grade centroblastic/immunoblastic	10 mg/kg	10 mg/kg x 1 dose	LTSF ^a	19 mos
	T09-03006	M	White	60	Hodgkin's; mixed cellularity histology	1 mg/kg	None	LTSF ^a	6.5 mos
	T22-11010	M	White	71	Mantle cell	10 mg/kg	10 mg/kg q 8wk	LTSF ^a	4 mos
CD	T16-08002	M	White	61	intermediate grade angiocentric B-cell lymphoma	10 mg/kg	Placebo	on-study	10.5 mos
	T21-32001	M	White	25	NK Lymphoma	5 mg/kg	Placebo	on-study	12.5 mos

^a LTSF = long-term safety follow-up

NHL = non-Hodgkin's lymphomas

NK = natural killer cell

4.1.2.6 Clinical Course of Patients Who Developed Lymphoproliferative Disease During Clinical Trials of Remicade or During Long-term Safety Follow-up

Narrative summaries are provided below for each of the six patients who developed a LPD during clinical trials of Remicade or during long-term safety follow up.

Patients with Rheumatoid Arthritis

Patient T22-05012 was a 74-year-old female with a 36-year history of RA. Prior to entering the clinical trial, she had a 15-year exposure history to MTX with doses reported between 7.5-15 mg/wk. She received concomitant corticosteroids and MTX during the study period. Her clinical course on study was complicated by development of pyelonephritis approximately 3 weeks after receiving the sixth (week 18) infusion of Remicade, which was treated with ciprofloxacin. One month later, she was later treated with fluconazole after a urine culture showed the presence of yeast. These complications were considered possibly related to Remicade. The patient continued to receive all scheduled Remicade infusions through week 26. One month after the last infusion, she developed renal failure, bilateral hydronephrosis, a left lung infiltrate, anemia, and confusion. CT scan revealed a diffuse infiltrative process in the retroperitoneum, which on biopsy was consistent with retroperitoneal fibrosis. Bilateral ureteral stent placements relieved the bilateral renal obstruction. The patient was treated symptomatically, and all events were considered life-threatening and possibly related to Remicade except bilateral hydronephrosis, which was considered probably not related to Remicade. Remicade was discontinued after week 26 of the study. At week 30, the patient developed anemia and thrombocytopenia. Bone marrow biopsy revealed a large B-cell lymphoma and staging evaluation revealed involvement of the bone marrow and pelvic and left inguinal lymph nodes. She was begun on cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and appeared to be responding well. However, after the fifth cycle of CHOP, the patient died suddenly at home (unwitnessed). Autopsy revealed continued presence of lymphoma, but lymphoma was not considered to be the cause of death.

Patient T07-01020 was a 48-year-old man with a 16-year history of rheumatoid arthritis who had been treated with prednisone, methotrexate, and azathioprine prior to entering the clinical trial. Cumulative exposure histories for these agents are not available. In the clinical trial, he received 2 infusions of Remicade (10 mg infusions separated by 2 weeks) together with prednisone. He responded to Remicade but eventually had disease progression, and methotrexate was reinitiated at a dose of 15 mg/wk. Eighteen months after the final Remicade infusion, he developed enlarged axillary and neck nodes. Biopsy results of a supraclavicular node showed a high-grade B-cell centroblastic/immunoblastic non-Hodgkin lymphoma. Records of his therapy for lymphoma are unavailable. The patient died ten months after diagnosis. Of note, the patient had a 12-year history of lymphadenopathy prior to study entry, and a supraclavicular lymph node that had been biopsied 12 years earlier (in 1981) revealed “reactive changes.” Moreover, an enlarged axillary lymph node was also noted and was reported to have decreased in size following

Remicade therapy. (This patient was discussed in Section 4.6.5.3.2 of Volume 39 of the BLA)

Patient T09-03006 was a 61-year old man with a 16-year history of rheumatoid arthritis who had been treated with gold, penicillamine and methotrexate prior to study entry. His cumulative methotrexate exposure history is not available. At study entry, splenomegaly was noted and considered to be secondary to Felty's syndrome, and was not evaluated further. During the study, he received only 1 infusion of Remicade at a dose of 1 mg/kg. Approximately 6.5 months after his only Remicade infusion, he developed an enlarged axillary lymph node that was biopsied and determined to be Hodgkin's lymphoma (mixed cellularity type). CT scans confirmed the axillary lymph node involvement, as well as splenomegaly and involvement of perivascular axillary nodes. The patient received a single cycle of cyclophosphamide, vincristine, procarbazine and prednisone (COPP) chemotherapy. His subsequent course was complicated by pneumonia and adult respiratory distress syndrome, and he died 9 months after his Remicade infusion. (This patient was discussed in Section 4.6.5.3.2 of Volume 39 of the BLA)

Patient T22-11010: information is forthcoming pending data ascertainment from the study investigator.

Patients with Crohn's Disease

Patient T16-08002 was a 61-year old man with a 30-year history of Crohn's disease. Prior to study entry, the patient had been treated for extended periods with prednisone (8 years), and he had an extensive azathioprine exposure history (6 years). Baseline lymphopenia was noted at the initial protocol screening ($0.28 \times 10^6/\text{mm}^3$) making him temporarily ineligible for the study. A repeat lymphocyte count 2 weeks later was $0.55 \times 10^6/\text{mm}^3$ and was acceptable for study enrollment. The etiology of his transient lymphopenia is not known. The patient received placebo at study entry, followed by a single open-label infusion of 10 mg/kg Remicade and 3 additional placebo infusions. Eight months after the patient's Remicade infusion, he developed fever, malaise, anemia, and thrombocytopenia. Abdominal CT showed splenomegaly and splenic and renal infarcts. Endoscopy of the upper gastrointestinal tract revealed duodenal ulcers and a polyp. Biopsy of the polyp showed an intermediate grade angiocentric B-cell lymphoma. He was treated with one cycle of CHOP chemotherapy. This first cycle of CHOP was complicated by disseminated Aspergillus infection, and the patient died 13 days following chemotherapy from cardiac failure and Aspergillus sepsis. (This patient was discussed in Section 4.6.5.3.2 of Volume 39 of the BLA.)

Patient T21-32001 was a 25-year-old white male with a 6-year history of CD at enrollment. The patient had had complete resection of the colon except for part of the sigmoid colon, and his disease was complicated by aphthous stomatitis and arthralgia. The patient had a 1-2 year exposure history to azathioprine. At the time of enrollment he was on a stable dose of prednisone. The patient received a single infusion of Remicade at 5 mg/kg and was subsequently randomized to the placebo maintenance group. The patient's course was complicated by a chronic hemolytic anemia and splenomegaly that

was considered by the investigator not related to Remicade. Histologic samples following splenectomy and bone marrow biopsy at week 54 of the study revealed a natural killer cell lymphoma with cytogenetic studies showing trisomy 8 and iso 7q in 5/20 metaphases. The patient was reportedly treated with etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin (VACOP-B) chemotherapy. Full chemotherapy records are not available. The patient was reported to show initial improvement with therapy, although, the patient died 19 months after study entry. (This patient was previously reported in the 30-week BLA.)

4.1.3 Registries

This section summarizes currently available information on lymphomas that have been reported in patients receiving Remicade in disease and drug registries.

4.1.3.1 National Database Registry of Rheumatoid Arthritis

Table 8 summarizes data obtained in January 2003 from the National Database Registry of Rheumatoid Arthritis. This registry is established and maintained by Dr. Fredrick Wolfe, who has been contracted by Centocor to create a RA safety registry. He has provided this preliminary data to Centocor under agreement.

- Of 18,417 patients enrolled in this registry, 90 have been diagnosed as having a lymphoma. Sixty-one of 90 patients were diagnosed as having lymphoma prior to the patients' enrollment in the registry, and 29 of 90 were diagnosed after the patients' enrollment.
- Among the 29 patients who developed lymphoma after enrollment, 9 patients had received Remicade, 8 patients received etanercept, 10 patients on MTX, and 5 patients received no Remicade, etanercept, or MTX.
- The proportion of patients who developed lymphomas among patients who received Remicade was comparable to the proportion among patients who received no Remicade, etanercept, or MTX.
- This is especially notable because patients receiving Remicade were on average 7 years older (70 ± 6.4 versus 63 ± 17.9 , respectively), and had a mean HAQ score that was substantially higher (1.56 ± 0.67 versus 0.68 ± 0.62 , respectively), suggesting a much higher inflammatory disease burden compared with the comparison patient group.
- It remains possible that lymphomas are under-reported in this registry. However, under-reporting would be much less likely to occur in patients who received Remicade because of the more frequent contact these patients have with health care providers in order to receive therapy.

Table 8 Lymphoma rates in patients enrolled in the National Database of Rheumatoid Arthritis

	Total Number of Patients Exposed	Lymphomas	Rate	Mean Age	% Male	Mean HAQ
All patients	18417	90	0.004887	68 ± 9.9	32%	1.36 ± 0.76
Pre-existing lymphoma	18417	61	0.003312	68 ± 9.7	23%	1.45 ± 0.76
Lymphomas after enrollment	18417	29	0.001575	68 ± 10.5	52%	1.16 ± 0.75
Drug exposure						
Remicade	6280	9	0.001433	70 ± 6.4	33%	1.56 ± 0.67
Etanercept	3403	8	0.002351	64 ± 7.3	63%	1.04 ± 0.91
Methotrexate	14176	10	0.000705	72 ± 9.5	60%	1.42 ± 0.68
No Remicade, etanercept, or MTX	3471	5	0.001441	63 ± 17.9	40%	0.68 ± 0.62

- The rate of lymphomas in patients who received Remicade was also comparable to the rates in patients who received etanercept (0.001433 versus 0.002351, respectively).
- This lower incidence in patients who received Remicade occurred despite the fact that these patients who received Remicade were on average 6 years older (70 ± 6.4 versus 64 ± 7.3 , respectively), and had a mean HAQ score that was higher by 0.42 (1.56 ± 0.67 versus 1.04 ± 0.91 , respectively).

MTX exposure was not associated with an increased rate of lymphoma. This is particularly interesting in view of studies that have implicated MTX therapy in the pathogenesis of lymphoma in some patients [Mariette, 2002; Salloum, 1996; Dawson, 2001; Stewart, 2001; Kingsmore, 1992; Taillan, 1993; Ellman, 1991; Kamel, 1993; Bachman, 1996; Georgescu, 1997]. Information on the percentage of patients treated with Remicade or etanercept who received concomitant MTX is not currently available.

4.1.3.2 The Therapy Resource Evaluation and Assessment Tool (TREAT™) Registry of Crohn's Disease

Table 9 and 10 summarize data obtained in the October 18, 2002 report on the TREAT Registry. The TREAT Registry, is a Centocor-sponsored safety registry, which evaluates the long-term clinical, economic and humanistic outcomes of various treatment regimens used in the management of Crohn's disease, including Remicade, in community-based

and academic practice settings. A variety of data are collected and analyzed via the Registry. This information includes demographics, changes in treatments, disease characteristics, adverse events, and serious adverse events. Patients will be followed for 4 to 5 years. The registry was begun in 1999, and this report contains a summary of data collected for 3638 patients and reflects the time-period through August 23, 2002. Both active patients and discontinued patients are included in this report.

Table 9 **Demographic summary of patients in the TREAT Registry**

	Number of Patients	Mean Age	% Male	% Mod- Severe Disease	% Severe- Fulminant Disease	Concomitant Immuno- modulatory Meds^a
Remicade- treated patients	1628	41.6 ± 14.1	41%	38%	3.1%	53.4%
Patients not exposed to Remicade	2010	44.4 ± 14.8	41%	13%	0.8%	36.6%
Total	3638					

^a Azathioprine, 6-mercaptopurine, methotrexate.

TREAT = The Therapy Resource Evaluation and Assessment Tool

Adverse events for patients in the TREAT Registry (for whom 6 months of follow-up data are available) are summarized in Table 10.

- Of 3638 patients enrolled in this registry,) 2 have developed a lymphoma: 1 of 1628 patients exposed to Remicade and 1 of 2010 patients not exposed to Remicade. Thus, the rate of lymphomas among patients who received Remicade was similar to that among patients who did not receive Remicade.
- This lack of association is notable because the Remicade-treated population was more severely ill than patients not treated with Remicade. In particular, at the time of registration, a greater percentage of Remicade-treated patients had moderate–severe (37.5% vs 13.0%; $p < 0.0001$) or severe-fulminant CD (3.1% vs 0.8%; $p < 0.0001$). Remicade-treated patients were also more likely at baseline to have been hospitalized in the previous year (29.4% vs. 20.5%; $p < 0.0001$), and were more likely to have undergone surgery in the previous year (19.8% vs. 14.5%; $p < 0.0001$). A greater percentage of Remicade-treated patients were taking prednisone (33.1% vs. 19.3%; $p < 0.0001$) and were more likely to be taking concomitant immunomodulatory drugs (53.4% vs. 36.6%; $p < 0.0001$). In addition, at the time of enrollment, these patients reported worse overall health ($p < 0.0001$) than patients with CD who were enrolled in TREAT and who did not receive Remicade. Each of these highlight a more severe

illness at baseline among patients treated with Remicade. Despite their more severe disease at baseline, patients treated with Remicade did not have a higher rate of lymphomas than disease-matched controls.

Table 10 Lymphomas in patients with CD enrolled in the TREAT Registry

	<u>Number of Patients^a</u>	<u>Lymphomas</u>	<u>Rate</u>
Remicade-treated patients	1108	1	0.000614
Patients not exposed to Remicade	1291	1	0.000498
Total	2399	2	0.00055

^a Only patients for whom 6-month follow-up data were received in 2002 are included.
TREAT = The Therapy Resource Evaluation and Assessment Tool

4.1.4 Postmarketing Reports

This section summarizes currently available information on lymphomas that has been reported in patients receiving Remicade in postmarketing experience. The information was obtained from Centocor's Integrated Summary of Safety for Remicade of August 9, 2002 and from Centocor's PSUR of October 17, 2002. A total of 71 cases of LPD have been collected in postmarketing reports, and these reports include spontaneous reports, LPD observed in clinical trials, and LPD collected in disease registries.

Demographics

A table illustrating demographics of the population of patients reported with LPD is presented in the Appendix B. These reports are from the following number of patients for each indication: RA (N=45; 63.4%), CD (N=20; 28.2%), or other/unknown indications (N=6; 8.5%). The ratio of females to males was equal. Among the CD population, the female:male:unknown gender ratio was 40.0%:55.0%:5.0%. Among the RA population, a female predominance occurred with a female:male:unknown gender ratio of 55.6%:44.4%:0.0%. The age range of the patients was from 18 to 84 years, and there were no pediatric cases. The mean age of the overall group was 58.2 years. These demographics are consistent with the characteristics of the underlying disease populations.

4.1.4.1 Distribution of Lymphoma Reports by Indication

The distribution of these cases by lymphoma type and indication is presented in Table 11. These cases were identified by querying JIPSY (Johnson and Johnson's Safety Database) using the 4 preferred terms under which LPDs were classified.

Table 11 **Distribution of lymphomas by type and indication**

Lymphoma Type by AE Term	Crohn's Disease		Rheumatoid Arthritis		Other/Unknown		Total	
	CD	%	RA	%	Other	%	Total	%
Lymphoma-like disorder	3	15.0	2	4.4	0	0.0	5	7.0
Lymphoma malignant	13	65.0	30	66.7	5	83.3	48	67.6
Non-Hodgkins lymphoma	4	20.0	12	26.7	1	16.7	17	23.9
Brain neoplasm malignant	0	0.0	1	2.2	0	0.0	1	1.4
Totals	20	100.0	45	100.0	6	100.0	71	100.0

The distribution of lymphomas by lymphoma type was approximately the same across indications. The majority of cases (N=48; 67.6%) were classified as malignant lymphoma. Of the lymphomas that were subcategorized as arising from B- or T-cell lineage (N=19), 15 (78.9%) were of B cell origin, and 4 (21.1%) were of T cell origin. Of the lymphomas in which information was provided to permit grading (Working Formulation) (N=12), 7 (58%) were low grade, 3 (25%) were intermediate grade, and 2 (17%) were high grade.

4.1.4.2 Latency

In the 47 cases in which sufficient information was available, latency since first exposure to Remicade was determined and is presented according to consecutive 60-day intervals following first exposure to Remicade. The largest number of LPD presented within 60 days of the first exposure to Remicade (Table 12).

Table 12 Latency (days) since first exposure by indication

Latency	RA	CD	Other	Total
Range	27 - 731	9 - 1096	30 - 388	9 - 1096
Mean	312.4	201.7	171	261.9
1: 60	4	8	1	13
61:120	4	0	1	5
121:180	2	1	0	3
181:240	3	0	0	3
241:300	2	0	0	2
301:360	2	0	0	2
361:420	7	3	1	11
421:480	2	0	0	2
481:540	1	0	0	1
541:600	1	0	0	1
601:660	2	0	0	2
661:720	0	0	0	0
721:780	1	0	0	1
781:840	0	0	0	0
> 840	0	1	0	1
Unk	14	8	2	24
Total	45	21	5	71

Postmarketing reports are likely biased towards an apparently shorter latency because reporters are more likely to associate recently administered drugs with an adverse event than medicines administered at times more remote from the event.

4.1.4.3 Other Suspect Drugs and Concomitant Medications Analysis

Unfortunately, in postmarketing reports, little information is available on the percentage of patients who had a history of exposure to conventional immunosuppressive agents used in RA and CD treatment. Information was available about other suspect drugs (N=10) and concomitant medications (N=24) in some patients, but no information is available for most patients. The data are provided in Table 13.

Table 13 Other suspect drugs and concomitant medication by indication

	RA	CD	Other	Total
Other suspect	5	5	0	10
Azathioprine	0	4	0	4
Ceftriaxone	1	0	0	1
Econazole	1	0	0	1
Mercaptopurine	0	1	0	1
Methotrexate	3	0	0	3
Concomitant medications	19	4	1	24
Azathioprine	3	4	0	7
Methotrexate	16	0	1	17

Exposure Analysis

When Centocor submitted the PSUR in October 2002, 344,000 patients had been exposed to Remicade worldwide. With 71 cases of lymphoma reported, the reporting rate was calculated to be 0.21 per 1,000 patients, and the reporting rates were the same for RA (0.21 per 1,000 patients) and CD (0.21 per 1,000 patients).

4.1.5 Discussion

Because of concern that has arisen from recent reports of LPD in patients receiving TNF α blocking agents, Centocor has compiled all available information on LPD in patients receiving Remicade. In addition, Centocor continues to 1) monitor data from our ongoing clinical trials and to assess the effect of Remicade on the occurrence of LPD, and large disease registries have been implemented by Centocor and 2) to further assess the potential effect of Remicade on the development of LPD in large cohorts of patients treated routinely in clinical practice. Although, these approaches have their limitations, as is discussed in detail below, they also provide useful information on the risk of lymphoid malignancy with these agents. A prospective randomized placebo-controlled study that accurately assesses the relationship between TNF α blocking agents and the incidence of LPD is not possible as it would require large numbers of patients to generate meaningful statistical data and the withholding of clinically efficacious agents from a population of patients with debilitating illnesses. Therefore, Centocor has collected and assessed as much other relevant data on this issue as possible to optimally assess this issue. It is important to note that concern has existed about the potential effect of TNF α blockers on lymphomas since their initial approval. At the FDA GI Advisory Committee in May 1998, when Remicade was recommended for approval in Crohn's disease, a presentation was made by Dr. Roger Cohen describing the cases of lymphoma in clinical trials to date. Of note, 4 of the 6 cases currently described in clinical trials were presented at the 1998 FDA GI Advisory Committee meeting. Centocor has been proactive in addressing this issue in its BLA and sBLAs and at each FDA Advisory Committee

meeting discussing Remicade. Moreover, Centocor has committed significant resources to studying the effect of Remicade on LPD, as evidenced by successful disease registries in both RA and CD.

Impact of Remicade on LPD Risk

The currently available information from clinical trials, postmarketing pharmacovigilance, and disease registries has been reviewed for any evidence that TNF α blocking agents, and specifically Remicade, might increase the risk of LPD.

Clinical Trials

Clinical trial data provide evidence that patients who received Remicade in clinical trials have a higher incidence of LPD than the general US population. It is not possible to meaningfully infer from this observation, however, that this observed rate is higher than might be expected *or* that the higher observed rates are secondary to exposure to Remicade. Rather, and importantly, the patient populations included in these clinical trials would be expected to have a higher baseline incidence of LPD compared with the general US population not only because of the existence of their underlying disease (either RA or CD), but also because of:

- 1) the duration and severity of their disease and
- 2) their previous and ongoing exposure to immunosuppressive agents.

Each of these latter variables can be reasonably expected to confer a higher risk for LPD incidence than is observed in the RA and CD populations as a whole. Data regarding the SIRs of MTX-naïve patients (SIR=0) versus DMARD, MTX-resistant patients (SIR=8.89) suggest a correlation between duration and severity of disease, exposure to chronic non- biologic immunosuppressive agents, and the existence of lymphoma (see Table 4). The data from Table 4, along with other data—including those related to the histologic type, temporal onset of disease, malignancy grade, postmarketing data (see below) and the presence of other plausible explanations for the current observed rates of lymphoma in clinical trials—may not support a likely association between Remicade use and the development of lymphoma.

Postmarketing Pharmacovigilance

Postmarketing pharmacovigilance has not revealed an increased risk of LPD in patients who were treated with Remicade. However, data captured in postmarketing may underestimate the true incidence of LPD in patients as a result of underreporting. This information may be more useful in examining the types of lymphomas that are reported. Importantly, a majority of the lymphomas for which information was available was low grade lymphomas. In clinical trials, where pathology reports are available, all six patients who developed lymphoma had distinct histologies, suggesting distinct pathophysiologic mechanisms and possibly initiating events. It is worth noting that high-grade non-Hodgkin lymphomas are most commonly seen among immunodeficiency-related lymphomas (e.g., post-transplant LPD), and only two high-grade lymphomas have been

reported in patients receiving Remicade. Information on the relationship between latency of LPD and Remicade exposure history is insufficient to determine whether Remicade contributed to the development of LPD.

Disease Registries

- In the National Database Registry of Rheumatoid Arthritis, patients with RA who received Remicade had a risk of LPD that was comparable to patients with RA who were never exposed to MTX or TNF α blocking agents.
- Likewise, in the TREAT Registry, the risk of LPD was similar in Remicade-exposed and non-exposed CD patients.
- These observations are noteworthy because the patients who received Remicade in each of these registries had a higher disease burden and disease activity than patients who did not receive Remicade.
- In patients with RA, high inflammatory activity is the variable shown to confer the highest odds ratio of LPD (Baecklund, 1998), so one might expect the rate of LPD to be higher in the populations of patients exposed to Remicade.

4.1.5.1 Comparison of the Effect of Different TNF α Blockers on LPD Incidence

- No head-to-head clinical trials comparing safety or efficacy of the three TNF α blockers have been performed.
- Although the SIRs obtained in clinical trials may be viewed by some as a surrogate of the effect of these agents on LPD incidence, this approach is fraught with fundamental methodological problems that create challenges in the interpretation of data.
- Different patient populations were studied in clinical trials of each of these agents, and it has been established that different patient characteristics may have dramatic effects on the risk of LPD (Baecklund, 1998).
- For example, much of the clinical trial data available for etanercept involved patients with MTX-naïve, early RA. Compared with the RA population as a whole, these patients were on average of younger age and had a relatively short duration of disease, no methotrexate or other immunosuppressive exposure, and a better functional class.
- In contrast, many of the patients enrolled in Remicade clinical trials were older patients, with long disease duration and who were only partially responsive to methotrexate. These patients also had, high inflammatory activity, prior exposure to multiple DMARDs (20% of whom were exposed to either azathioprine or cyclosporine), and poor baseline functional status.

- The baseline LPD risk in each of these populations is likely to differ significantly and would seriously confound any comparisons of SIRs derived from clinical trial experience. The effect of targeting these sub-populations is observed in sub-analyses of data from patients enrolled in Remicade clinical trials.
- Thus, it is scientifically and medically inappropriate to draw comparisons of SIRs of different products given the vastly different patient populations studied and the multiple inherent confounding factors.
- Data that partially address the effect of the safety of the various TNF α blockers in comparable patient populations may exist in the National Database Rheumatoid Arthritis Disease Registry, a collection of information in this area on a large cohort of patients treated with Remicade and etanercept.
- In this registry, the risk of lymphomas in patients treated with Remicade or etanercept was low (0.001433 versus 0.002351, respectively). It is interesting to note that incidence of lymphoma in patients who received Remicade compared favorably with patients who received etanercept despite their older mean age (70 ± 6.4 versus 64 ± 7.3 , respectively), and their greater disability as measured by HAQ score (mean 1.56 ± 0.67 versus 1.04 ± 0.91 , respectively). However, the data are limited with regard to the inferences one might draw from these data, in part because it is not known if all other patient characteristics were similar or of comparable treatment or follow-up duration.

Summary

- Evidence presented herein supports previous reports that the incidence of LPD in patients with RA and CD is higher than that observed in the general US population.
- Disease characteristics such as age, disease duration, exposure to conventional immunosuppressive agents, and most importantly, disease and inflammatory burden may further increase LPD risk in sub-populations of patients with CD and RA.
- These factors must be carefully considered when assessing the influence that TNF α blockers may have on the incidence of LPD.
- Continued vigilance is warranted until the relationship of these agents to LPD incidence can be fully characterized. Centocor continues to examine the evidence of potential effects of Remicade on the occurrence of LPD in clinical trials, through postmarketing pharmacovigilance, and in large RA and CD disease registries.

4.2 Non-Lymphoproliferative Malignancies/Solid Tumors

This section will summarize non-lymphoproliferative disease (non-LPD) malignancies reported in Remicade clinical trials and postmarketing experience. The clinical trial reports will be examined by indication (CD or RA) for the period study participation and post-study follow-up of up to 3 years.

The postmarketing reports will be cumulative from August 24, 1998 to August 23, 2002.

4.2.1 Clinical Trial Data

In interpreting this information, it is important to note that the number of patients treated with Remicade (N = 1,678) is greater than the number included in the control population (N = 192). During completed Centocor-sponsored clinical studies, 14 (1.0%) Remicade-treated patients developed a non-LPD malignancy and 1 (0.5%) placebo-treated patient developed a non-LPD malignancy.

Nonlymphoproliferative Malignancies Reported During Study Participation

Studies in Crohn's Disease

Among the 580 patients treated with Remicade in ACCENT I, 5 (0.9%) patients had a non-LPD malignancy. One each of the following types of neoplasm were observed: adenocarcinoma (bilateral hypernephroma), basal cell carcinoma, bladder carcinoma, malignant skin neoplasm, and malignant breast neoplasm. Of the 306 patients treated with Remicade in ACCENT II, none had a non-LPD malignancy.

In CD studies other than ACCENT II or ACCENT I, no Remicade-treated patient developed a non-LPD malignancy while on study.

Studies in Rheumatoid Arthritis

During the ATTRACT study, 9 patients developed a non-LPD malignancy. Among the 9 patients with non-LPD malignancies the following types of cancer were reported: recurrent breast cancer (1 patient), rectal carcinoma (1 patient), malignant melanoma (1 patient), squamous cell skin carcinomas (2 patients, one of whom received placebo), and basal cell skin carcinomas (3 patients). In addition, one patient reported both a squamous cell skin carcinoma and a malignant melanoma. In the other five RA studies with Remicade, one case of breast cancer was reported.

Nonlymphoproliferative Malignancies Reported During Long-term Safety Follow-up

In the post-study long-term follow-up of all Centocor-sponsored studies through three years, 13 Remicade-treated patients reported a non-LPD malignancy versus 4 placebo-treated patients. In Centocor-sponsored studies not included in the database, non-LPD malignancies have been reported in 6 patients. A summary of non-LPD malignancies

that have been reported to Centocor for any patient who participated in a completed Centocor-sponsored study of Remicade and non-LPD malignancies reported during 3 years of long-term safety follow-up, is presented in Table 14.

Patients with Crohn's Disease

During the long-term safety follow-up period in patients with CD, 1 non-melanoma skin cancer (Remicade-treated patient) and 7 other malignancies were reported (5 in Remicade-treated patients and 2 in patients who received placebo). Among the five Remicade-treated patients who had malignancies, the following types of cancer were reported: papillary thyroid carcinoma (1 patient), prostate cancer (1 patient), skin cancer (1 patient), adenocarcinoma of the colon and signet cell colon carcinoma (Dukes C1, 1 patient). Among placebo-treated patients who had malignancies, the following types of cancer were reported: one spindle cell and one clear-cell, renal carcinoma.

Patients with Rheumatoid Arthritis

Six Remicade-treated patients with RA had non-LPD malignancies reported during the 3-year follow-up period. The non-LPD malignancies for these 6 patients, who were reported in previous marketing applications, include the following types of cancer: malignant lung neoplasm (1 patient), Clark's level II superficial spreading melanoma (1 patient), basal cell carcinoma of the skin of the lower left leg (1 patient), melanoma (1 patient), prostate cancer (1 patient), and ovarian cancer (1 patient).

In addition, non-LPD malignancies were reported in 2 placebo-treated patients during the 3-year follow-up period. One patient had malignant melanoma and uterine cancer, and the other colon cancer.

Table 14 Summary of subjects with 1 or more non- lymphoproliferative disease malignancies who participated in Centocor-sponsored Remicade clinical studies^a

	CD Studies		RA Studies		All Studies	
	Placebo	Remicade	Placebo	Remicade	Placebo	Remicade
During study						
Non-melanoma skin cancers	0	2	1 ^b	5 ^c	1 ^b	7 ^c
Other malignancies	0	3	0	5 ^c	0	8 ^c
Long-term follow-up (up to 3 yrs after treatment)						
Non-melanoma skin cancers	0	1	0	1	0	2
Other malignancies	2	5	2 ^b	6	4 ^b	11
Total non- lymphoproliferative disease malignancies						
Total non-melanoma skin cancers	0	3	1 ^b	6 ^c	1 ^b	9 ^c
Total other malignancies	2	8	2 ^b	11 ^c	4 ^b	19 ^c
Total non- lymphoproliferative disease malignancies	2	11	2 ^b	17 ^c	4 ^b	28 ^c

^a Includes malignancies in Datasets 1,2,3, and during 3 years of long-term follow-up.

^b Subject C0168T22-27005 had both nonmelanoma skin cancer and a melanoma (counted under “other malignancy”); this subject is counted once in the Total malignancies row.

^c Subject C0168T22-27008 had both nonmelanoma skin cancer and a melanoma (counted under “other malignancy”); this subject is counted once in the Total malignancies row.

RE125:IS_MAL_1117 May 2002, 12:30:51 PM

A review of the medical literature has not demonstrated consistently an increased risk for non-LPD malignancies in the RA or CD population as has been observed for LPD malignancies. No increased risk for non-LPD malignancies in Remicade-treated RA or CD patients was observed when incidence rates were compared with those of the general US population as reported in the 1999 SEER database. Attached are two tables for non-LPD malignancies from our clinical study population. The SEER database was used to calculate standardized incidence rate (SIR) for both Remicade-treated and placebo patients. Table 15 and Table 16 contain the expected numbers of cases, SIR values, and 95% confidence intervals for the SIR value, based on the 1999 SEER database for Remicade-treated and placebo patients, respectively. The expected numbers of cases are adjusted for age, gender, and race.

Table 15 **Number of observed and expected non-lymphoma malignancies ^a in Remicade treated subjects; 1999 SEER, adjusted for age, gender and race**

Population	Number of Subjects (N)	Total Subject-years Follow-up	Median Subject-years Follow-up	Observed Number of Cases	Expected Number of Cases	Standardized Incidence Rate (SIR)	SIR 95% CI ^b
All studies	1678	3445.2	1.42	19	17.80	1.07	[0.64, 1.67]
All Crohn's disease studies	1106	1646.2	1.37	8	4.61	1.74	[0.75, 3.42]
All rheumatoid arthritis studies	555	1755.8	3.30	11	13.10	0.84	[0.42, 1.50]
All rheumatoid arthritis subjects with MTX	415	1336.5	3.51	10	9.95	1.01	[0.48, 1.85]
All rheumatoid arthritis subjects without MTX	140	419.3	3.10	1	3.15	0.32	[0.01, 1.77]

^a Excludes non-melanoma skin cancers, which are not included in the SEER database.

^b Confidence intervals based on exact method.

SEER = Surveillance Epidemiology and End Results

SIR = standardized incidence rate (ratio)

Table 16 **Number of observed and expected non-lymphoma malignancies^a in placebo treated subjects; 1999 SEER, adjusted for age, gender and race**

Population	Number of Subjects (N)	Total Subject-years Follow-up	Median Subject-years Follow-up	Observed Number of Cases	Expected Number of Cases	Standardized Incidence Rate (SIR)	SIR 95% CI^b
All studies	192	411.7	3.00	4	2.22	1.80	[0.49, 4.61]
All Crohn's disease studies	56	94.8	2.45	2	0.18	11.11	[1.35, 40.14]
All rheumatoid arthritis studies	133	309.9	3.00	2	2.02	0.99	[0.12, 3.58]
All rheumatoid arthritis subjects with MTX	109	301.4	3.12	2	1.98	1.01	[0.12, 3.65]
All rheumatoid arthritis subjects without MTX	24	8.5	0.10	0	0.04	0	NC ^c

^a Excludes non-melanoma skin cancers, which are not included in the SEER database.

^b Confidence intervals based on exact method.

^c NC – Not calculated

SEER = Surveillance Epidemiology and End Results

SIR = standardized incidence rate (ratio)

There is no marked increase in non-LPD malignancies in patients treated with Remicade in these comparisons. Non-LPD malignancies occurred in a small number of patients, many with predisposing factors for malignancies. Patients continue to be monitored for 3 to 5 years after study participation in order to better understand the etiology of malignancy in Remicade-treated patients. Continued surveillance and monitoring of the reporting frequency of non-LPD malignancies is warranted to ensure that the observed rate of reporting is similar to what is expected in these patient populations.

4.2.2 Postmarketing Data

4.2.2.1 Overview

This section will provide a review of the cumulative data reported in postmarketing. In this section, a tabulation of the non-LPD cancers by type is provided for the cumulative data set of non-LPD cancers.

4.2.2.2 Cases Received Cumulatively, 24 August 1998 through 23 February 2002

All analyses in the remainder of this section are based on the cumulative data set of cancers.

4.2.2.2.1 Distribution of Malignancies

Three hundred fifty-four non-LPD malignancies have been reported in the postmarketing database through 23 August 2002. Non-LPD malignancies represent a subset of all neoplasms (which include benign neoplasms as well as LPD malignancies). The most frequently reported malignancies were skin cancer (N=77; 15.9%), gastrointestinal (GI) cancers (N= 68; 14.1%), breast cancer (N=58; 12.0%), and respiratory cancers (N=53; 11.0%). The following presentation (Table 17) shows the distribution by indication.

Table 17 Cumulative non- lymphoproliferative disease malignancy by indication

Malignancy	RA	CD	Other	Unk	Total
Breast	49	3	2	4	58
CNS	7	0	1	1	9
Endocrine	4	0	0	1	5
Genital	23	7	4	3	37
GI	35	27	0	6	68
Leukaemia	11	6	1	3	21
Musculoskeletal	0	1	1	0	2
NOS	6	0	0	2	8
Respiratory	39	8	0	6	53
Skin	49	13	3	12	77
Urinary	7	3	3	3	16
Total	230	68	15	41	354

NOS = not otherwise specified

When normalized for the numbers of patients who received Remicade, malignant gastrointestinal neoplasms appeared to be more frequently reported among patients with CD than patients with RA. This is consistent with the observation that chronic inflammation of the bowel increases the risk of gastrointestinal malignancy in the CD population (Bernstein et al. 2000).

4.2.2.2.2 Latency

Information was available in 403 cumulative cases to allow determination of the interval between the onset of treatment with Remicade and the diagnosis of the any cancer. This table includes LPD as well as non-LPD malignancies. The latency period from the first exposure to Remicade according to the indication for the cumulative experience is presented below. The latency is presented according to consecutive 60-day intervals following first exposure to Remicade (Table 18).

Table 18 Latency (days) since first exposure by indication, cumulative experience

Latency	RA	CD	Other	Unk	Total
1: 60	41	22	3	3	69
61:120	28	17	2	4	51
121:180	19	7	2	2	30
181:240	14	2	3	1	20
241:300	23	1	3	4	31
301:360	12	3	3	0	18
361:420	21	6	0	0	27
421:480	4	2	0	1	7
481:540	5	3	1	2	11
541:600	3	0	1	2	6
601:660	7	3	0	1	11
661:720	2	0	0	1	3
721:780	8	1	0	0	9
781:840	0	0	0	1	1
> 840	2	4	0	1	7
Unk	111	36	6	29	182
Total	300	107	24	52	483

Of the 301 cumulative cases with available information, 69 (22.9%) occurred within 60 days, 120 (39.9%) within 120 days and 150 (49.8%) within 180 days of the onset of treatment. Similar patterns for latency were observed for both RA and CD. It is highly unlikely that all of the events necessary for carcinogenesis could occur in this time frame. However, the data are insufficient to address whether or not exposure to anti-TNF agents can affect one specific carcinogenic event or accelerate the growth of existing tumors.

In an effort to assess the effect of concomitant immunosuppressive agents of the reporting rates for neoplasms, crude proportional reporting rates for neoplasms from the safety database were analyzed. These rates were calculated for Remicade and the three most often used immunosuppressive agents used in combination with Remicade (i.e., MTX, azathioprine and 6-mercaptopurine). The proportional rate for Remicade was very close to the proportion for all reports (2.7% for Remicade alone vs. 2.3% for the whole safety database), whereas for the combined group of the three immunosuppressive agents without Remicade, the proportional rate was 11.6%.

4.2.3 Labeling

4.2.3.1 Precautions Section

Malignancy

Patients with long duration of Crohn's disease or rheumatoid arthritis and chronic exposure to immunosuppressant therapies are more prone to develop lymphomas (see ADVERSE REACTIONS, Malignancies/Lymphoproliferative Disease). The effect of treatment with Remicade on these phenomena is unknown.

4.2.3.2 Adverse Reactions Section

Malignancies/Lymphoproliferative Disease

In completed clinical studies of Remicade for up to 102 weeks, 18 of 1372 patients developed 19 new or recurrent malignancies of various types over 1430 patient-years of follow-up. These were non-Hodgkin's B-cell lymphoma, breast cancer, melanoma, squamous, rectal adenocarcinoma, and basal cell carcinoma. There are insufficient data to determine whether Remicade contributed to the development of these malignancies. The observed rates and incidences were similar to those expected for the populations studied^{10,11} (see PRECAUTIONS, Malignancy).

4.2.4 Discussion and Conclusions

The pattern and incidence of non-LPD malignancies in the clinical trial and postmarketing Remicade databases is similar to that seen in the general population as represented in the SEER database. For certain histologies reported, (e.g., breast, colon, prostate) the normal tumor initiation and growth rates are such that the short interval between Remicade treatment and cancer diagnosis makes a causal association less likely.

In conclusion, additional long-term monitoring and follow-up is warranted. Centocor continues to monitor Remicade's effect on non-LPD malignancies in clinical trials, postmarketing surveillance, and in large RA and CD disease registries.

4.3 Tuberculosis and Opportunistic Infections

4.3.1 Tuberculosis

The number of TB cases reported in clinical trials with Remicade, as well as postmarketing reports, will be presented in this section. The effect of a Centocor-sponsored TB education program will also be discussed.

4.3.1.1 Clinical Trial Data

Data presented in this section are derived from completed Centocor-sponsored trials through 31 May 2002. A more comprehensive review of TB cases covering additional ongoing, blinded studies has been submitted separately to the FDA. A total of three patients treated with Remicade were reported to have TB in completed, Centocor-sponsored studies in the period through 31 May 2002. One patient in ATTRACT (of 428 patients in the pivotal RA trial), 1 patient in ACCENT I (of 580 patients in the Crohn's maintenance therapy trial), and 1 patient in PROMPT (of 553 patients in a Phase 3b RA trial). In addition, a current update for ongoing trials was submitted to the FDA for review.

4.3.1.2 Postmarketing Data

In postmarketing experience, a greater than expected number of cases of disseminated TB has been reported in patients within 6 months of treatment with Remicade. This suggests that treatment with Remicade may increase the risk of activating latent TB. As a result, Centocor has modified the labeling for the product and mandated that all patients be screened for active and latent TB prior to initiation of Remicade therapy.

4.3.1.2.1 *Cumulative Surveillance (23 August 1998 through 23 August 2002)*

Surveillance statistics of TB cases have been reported on a cumulative basis for patients who have received Remicade therapy since the approval in the US on August 24, 1998. Within this time period, there have been 86 cumulative cases of TB reported in the US and 191 cases of TB reported outside of the US among patients treated with Remicade. There are distinct regional and geographical differences in reports of TB associated with Remicade therapy.

4.3.1.2.1.1 Tuberculosis Reports in the United States

Of the 86 TB cases reported in the US during this cumulative reporting period, 55 cases were reported in patients with rheumatoid arthritis, 18 cases were reported in patients with Crohn's disease, and 13 cases were reported in patients whose disease indication

was unknown. While Remicade experience in the US accounts for 64% of worldwide patient exposure, reported TB cases in the US account for only 31% of all reported cases worldwide (Table 19). The cumulative rate of TB in the US is 0.2 per 1,000 patients-year of exposure.

Table 19 Exposure data for cumulative tuberculosis reports by region

	<u>US</u>	<u>%</u>	<u>EU</u>	<u>%</u>	<u>Total</u>
Cumulative exposure	233,547	64.1	103,335	28.2	365,201
Cumulative tuberculosis cases	86	31.0	156	56.3	277
Cumulative patient-years follow-up	411,336		113,652		554,372
Reporting rate per 1,000 patient-years exposure	0.2		1.4		0.5

EU = European Union

The percentages for the EU and US do not total 100%, since countries outside the EU and US are not presented in this table.

4.3.1.2.1.2 Tuberculosis Education Program

During August and September 2001, a Centocor-sponsored TB education program was conducted in the US with the following objectives: 1) to inform physicians of revised labeling regarding the risk of reactivation of latent TB in patients receiving Remicade and 2) to provide education on the need to screen patients for latent TB by tuberculin skin testing and the need to initiate anti-TB treatment in patients who tested positive for latent TB before starting treatment with Remicade. Five thousand physicians were targeted for this education program. A follow-up study was conducted to measure the effectiveness of the education program by auditing rheumatology practices in the US to determine the percentage of patients who were being tested for TB before starting treatment with Remicade.

During the follow-up study, medical records of patients who began anti-TNF- α therapy (Remicade or etanercept) after 01 October 2001 were reviewed at 124 rheumatology practices. Information was obtained for 414 patients who received Remicade and 380 patients who received etanercept. Overall, 80% of patients who received Remicade had a skin test performed, and 40% of patients who received etanercept had a skin test performed. Approximately 2% of patients who had tuberculin skin tests were positive for latent TB and subsequently received anti-TB therapy.

The results of the follow-up study indicate that the US education program was successful in promoting the need for physicians to perform skin tests for latent TB and to administer anti-TB therapy when necessary before initiating Remicade therapy. Importantly, the high percentage of patients being tested for TB prior to receiving Remicade coincides

with a continuous decline in the number of spontaneous reports of active TB in the US over the last nine months (see Figure 1 below).

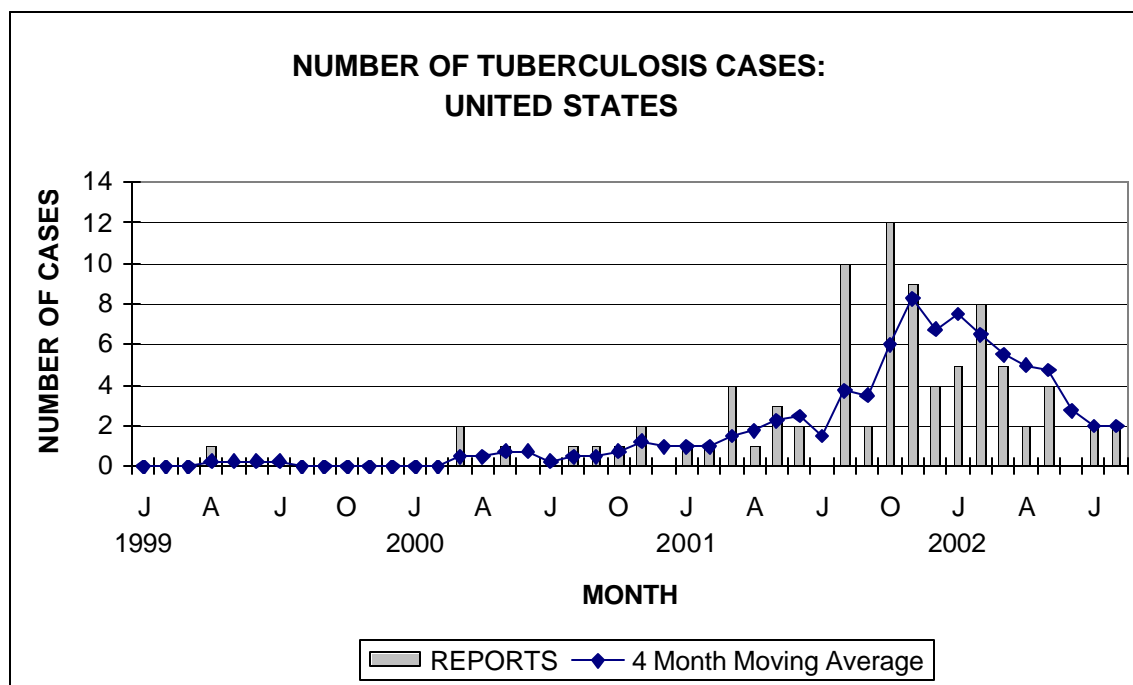


Figure 1 Cumulative tuberculosis cases: United States (24 August 1998 – 23 August 2002)

4.3.1.2.1.3 Tuberculosis Cases Outside of the United States

The EU countries with the largest number of TB reports were Spain (52), France (41), Italy (14), Germany (11), and Belgium (10). From the cumulative experience (Table 19), there were 156 TB case reported in the EU, which resulted in a cumulative rate of 1.4 reports per 1,000 patient-years of exposure. The cumulative reporting rate for TB in the US is 0.2 per 1,000 patient-years of exposure. This difference highlights what likely reflects the regional differences in TB exposure and the earlier effect of education programs.

In the EU, educational programs were conducted throughout Europe in early 2002 to educate Remicade prescribers regarding the risks and screening procedures for TB. The results of the educational effort in Europe are reflected by the declining trend in new reports of TB in the EU.

4.3.1.3 Labeling

Current Remicade labeling include the following sections in Boxed Warning and Bolded Warnings on TB and opportunistic infections:

WARNING**RISK OF INFECTIONS**

TUBERCULOSIS (FREQUENTLY DISSEMINATED OR EXTRAPULMONARY AT CLINICAL PRESENTATION), INVASIVE FUNGAL INFECTIONS, AND OTHER OPPORTUNISTIC INFECTIONS, HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. SOME OF THESE INFECTIONS HAVE BEEN FATAL (SEE WARNINGS).

PATIENTS SHOULD BE EVALUATED FOR LATENT TUBERCULOSIS INFECTION WITH A TUBERCULIN SKIN TEST.¹ TREATMENT OF LATENT TUBERCULOSIS INFECTION SHOULD BE INITIATED PRIOR TO THERAPY WITH REMICADE.

4.3.1.3.1 *Bolded Warnings Section:*

WARNINGS**RISK OF INFECTIONS**

(See boxed WARNING)

SERIOUS INFECTIONS, INCLUDING SEPSIS HAVE BEEN REPORTED IN PATIENTS RECEIVING TNF-BLOCKING AGENTS. SOME OF THESE INFECTIONS HAVE BEEN FATAL. MANY OF THE SERIOUS INFECTIONS IN PATIENTS TREATED WITH REMICADE HAVE OCCURRED IN PATIENTS ON CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO THEIR CROHN'S DISEASE OR RHEUMATOID ARTHRITIS, COULD PREDISPOSE THEM TO INFECTIONS.

REMICADE SHOULD NOT BE GIVEN TO PATIENTS WITH A CLINICALLY IMPORTANT, ACTIVE INFECTION. CAUTION SHOULD BE EXERCISED WHEN CONSIDERING THE USE OF REMICADE IN PATIENTS WITH A CHRONIC INFECTION OR A HISTORY OF RECURRENT INFECTION. PATIENTS SHOULD BE MONITORED FOR SIGNS AND SYMPTOMS OF INFECTION WHILE ON OR AFTER TREATMENT WITH REMICADE. NEW INFECTIONS SHOULD BE CLOSELY MONITORED. IF A PATIENT DEVELOPS A SERIOUS INFECTION, REMICADE THERAPY SHOULD BE DISCONTINUED (see ADVERSE REACTIONS, Infections).

CASES OF HISTOPLASMOSIS, LISTERIOSIS, PNEUMOCYSTOSIS AND TUBERCULOSIS, HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. FOR PATIENTS WHO HAVE RESIDED IN REGIONS WHERE HISTOPLASMOSIS IS ENDEMIC, THE BENEFITS AND RISKS OF REMICADE TREATMENT SHOULD BE CAREFULLY CONSIDERED BEFORE INITIATION OF REMICADE THERAPY.

4.3.2 Opportunistic Infections

4.3.2.1 Clinical Trial Data

Safety data reported to Centocor through 31 May 2002 are described for ongoing controlled and uncontrolled Centocor-sponsored studies. One opportunistic infection (OI) is reported from Centocor trials for this period. In ATTRACT, one patient with RA was reported to have a case of coccidioidomycosis from a study site in Arizona.

4.3.2.2 Postmarketing Data

4.3.2.2.1 *Overview*

Opportunistic infection statistics reported during the postmarketing surveillance period have been accumulated since the US approval date of 24 August 1998. The data presented here for opportunistic infections is from 24 February 2002 to 23 August 2002, the most recent complete collection period.

An estimated 44,000 patients in the EU/Norway and 113,000 patients in North America were exposed to Remicade during this data collection period. In Japan, where Remicade was recently approved for Crohn's disease, 1,000 patients were treated during this time period. In the remaining countries of the world, 4,000 patients were treated. Therefore, an estimated 163,000 patients were exposed to Remicade worldwide during this reporting period.

4.3.2.2.2 *Surveillance (24 February 2002 through 23 August 2002)*

Opportunistic infections that were reported during this surveillance period are summarized in Table 20.

Table 20 Potentially opportunistic infections

Pathogen	Number Cases	Deaths	Geographic Location		Indication			Report Type	
			North America	EU & Norway	Crohn's	RA	Other ¹	New	Follow-up
Pneumocystis carinii pneumonia	10	2	4	4	1	1	6	8	2
Salmonellosis	1	0	0	1	1	0	0	1	0
Atypical mycobacteria	20	0	13	7	1	15	4	17	3
Histoplasmosis	8	1	8	0	2	4	2	7	1
Listeriosis	9	3	5	4	4	4	1	6	3
Aspergillosis	13	3	6	7	1	8	4	12	1
Coccidioidomycosis	9	4	6	0	0	3	2	5	0
CMV infections	6	1	3	3	1	1	4	5	1
Cryptococcosis	8	0	9	0	2	3	4	8	0
Systemic candidiasis	4	0	1	3	2	1	1	3	1
Mucormycosis	1	0	1	0	0	1	0	1	0
Toxoplasmosis	4	0	3	1	0	2	1	3	0

¹ Other includes unknown indications.

CMV = cytomegalovirus

EU = European Union

4.3.2.3 Labeling

For labeling information on opportunistic infection, refer to Section 4.3.1.3.

4.3.2.4 Discussion

Opportunistic infections have been reported in association with Remicade therapy. Atypical mycobacterial infections appear to be reported more frequently in patients with RA than patients with CD, and while the reason for this is not known, possibilities include the altered immune response associated with RA or other factors (eg, co-morbid conditions, age, or concomitant medication usage). Overall, compared with previous reporting periods and considering the increased usage of the drug, the pattern remains unchanged. Active monitoring for potential opportunistic infections is ongoing.

4.3.3 Overall Conclusions

The use of Remicade is associated with an increase risk for reactivation of latent TB. The risk has been recognized and is included as a bolded warning in the Remicade prescribing information. Results from the preventive efforts in the United States indicate that TB case reporting totals decreased following implementation of a preventive education program. The higher prevalence of latent TB in some areas of the EU and in other territories is reflected in the higher risk of TB reactivation in those countries. However, ongoing activities aimed at provider education and the assessment of program effect coupled with ongoing monitoring will be needed continue to assess TB risk.

Reported rates for cases of opportunistic infection in are similar to those provided in previous reports.

4.4 Neurological Events

4.4.1 Demyelinating Disorders

4.4.1.1 Clinical Trial Data

In Centocor-sponsored clinical studies (ie, for completed and ongoing, controlled and uncontrolled, and during 3 years of long-term safety follow-up), there were 5 cases of multiple sclerosis/demyelinating disease, each occurring in patients with CD, and 1 case of Guillain-Barre syndrome that occurred in an RA patient.

4.4.1.2 Postmarketing Data

Surveillance data for neuropathic conditions from 24 August 1998 to 23 August 2002 are summarized in Table 21 and include reported cases of neurological disorders.

In order to assess cases of neurological disorder, reports were grouped into four neurologic events/event groups, and included central demyelination, Guillain-Barre Syndrome (GBS)/chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), neuropathy, and transverse myelitis.

Table 21 Postmarketing surveillance data for neuropathic conditions

Event/ Event Group	New Cases	Follow-up Cases
Central demyelination	15	6
GBS/CIDP	4	5
Neuropathy	27	10
Transverse myelitis	1	0
Total number of unique cases identified*	44	20

* More than one relevant event was reported in several cases.

4.4.1.2.1 Results

4.4.1.2.1.1 Central Demyelination

There were a total of 21 reported cases of central demyelination. Eleven cases of central demyelination were reported in the US. Among patients with central demyelination for

whom the indication was known, 3 were treated for Crohn's disease and 12 were treated for rheumatoid arthritis. Two patients had a history of pre-existing multiple sclerosis.

Guillain-Barre Syndrome (GBS)/Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIPD): There were 9 reported cases of GBS or CIPD variant of peripheral demyelination. All 9 reported cases occurred in females ranging in age from 20 to 66 years. Four patients were being treated for rheumatoid arthritis, 3 for Crohn's disease, 1 for psoriatic arthritis and ankylosing spondylitis, and 1 for ankylosing spondylitis. In 1 patient, the events recurred after subsequent treatment with etanercept and in 1 patient, concurrent malignant melanoma was also reported.

Neuropathy: There were 31 reported cases of neuropathy and 6 additional cases of neuropathy were reported in patients who had other neurologic syndromes that have been described elsewhere in this document. Among patients for whom neuropathy was reported as a primary event, 15 were treated for rheumatoid arthritis, 10 were treated for Crohn's disease, and 1 was treated for psoriatic arthritis. The indication was unknown for 5 patients. The outcome was unknown in 19 cases, resolved in 5 cases, improved in 3 cases, and persisted in 4 cases.

Transverse Myelitis: One initial case of transverse myelitis was reported during this period for a patient with rheumatoid arthritis who was treated with Remicade.

4.4.1.3 Labeling

4.4.1.3.1 Warnings Section

Neurologic Events

Remicade and other agents that inhibit TNF have been associated in rare cases with optic neuritis, seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis. Prescribers should exercise caution in considering the use of Remicade in patients with pre-existing or recent onset of central nervous system demyelinating or seizure disorders.

4.4.1.3.2 Labeling Supplement

Based on postmarketing adverse event reports of transverse myelitis, Centocor has submitted a labeling supplement on January 13, 2003, to add "transverse myelitis" to the postmarketing adverse reactions section of Remicade labeling.

4.4.1.4 Discussion

A total of 64 unique cases reporting central demyelination, GBS/CIDP, neuropathy and transverse myelitis were identified for assessment. Of these, 44 cases were identified in this reporting period, and 20 were follow-up cases. The indication for treatment in the majority of cases was rheumatoid arthritis. Many cases may have been confounded by treatment indication, concurrent infection, medical history, or concomitant medication

usage. In particular, rheumatoid vasculitis or cerebral arteriosclerosis may have contributed to cases of central demyelination or GBS cases. Mechanical complications/autoimmune phenomena (rheumatoid arthritis) and malabsorption syndromes/nutritional deficiencies (CD) may have been associated with some cases of peripheral neuropathy.

4.4.2 Optic Neuritis

4.4.2.1 Clinical Trial Data

Two cases of optic neuritis, both in patients with CD, were reported in Remicade clinical trials.

4.4.2.2 Postmarketing Data

4.4.2.2.1 Cumulative Experience (24 August 1998 through 23 August 2002)

A search and review of all reports of optic neuritis and optic neuropathy in the drug safety database was conducted to identify all adverse events reports related to optic neuritis. Thirty-four cases of optic neuritis were identified, the majority (25 of the 31 whose indication for use was known) of which involved patients who were being treated for rheumatoid arthritis (80.6%) (see Table 22). There were no deaths or life-threatening events among the 34 reported cases. The country of origin for the reports included Canada (3), France (1), Germany (1), the Netherlands (3), Spain (1), and the United States (25).

Table 22 Demographics of cumulative reports: optic neuritis

Characteristic		Rheumatoid Arthritis # of Cases (N = 25)	Crohn's Disease # of Cases (N = 3)	Other/Unknown Indications ¹ # of Cases (N = 6)	Total (N = 34)
Gender	Male	8	3	2	13
	Female	17	0	1	18
	Unknown	0	0	3	3
Age	≤ 17	0	0	0	0
Range: 27 - 74	18 - 64	17	3	3	23
	≥ 65	6	0	0	6
Mean: 52	Unknown	2	0	3	5

¹ Other indications include psoriatic arthritis (N=2) and inflammatory spondyloarthropathy (N=1).

4.4.2.3 Labeling

For labeling information on opportunistic infection, refer to Section 4.4.1.3.

4.4.2.4 Discussion

Optic neuritis is a relatively rare condition, which can be associated with many medical conditions including rheumatoid arthritis, ankylosing spondylitis, and Crohn's disease. It has been hypothesized that the rare cases of optic neuritis and ischemic optic neuropathy appearing in the rheumatoid arthritis population are a manifestation of vasculitis or an underlying inflammatory process occurring in the optic nerve.

4.4.2.4.1 Conclusions

The neurological events in many cases may have been confounded by treatment indication, comorbidity, medical history, and/or concomitant medication usage; however, the quantitative contribution of such effects is difficult to determine from surveillance data alone.

4.5 Congestive Heart Failure

Preclinical and early clinical data suggested that the cytokine, TNF α plays a role in the pathogenesis and progression of congestive heart failure (CHF). Chronic infusion of TNF α was shown to produce left ventricular contractile dysfunction and dilatation in rats (Yokoyama et al, 1993) and transgenic mice with overproduction of myocardial TNF α developed ventricular dilatation and systolic dysfunction (Kubota et al, 1997; Bryant et al, 1998). One potential issue with these studies however is that the CHF induced in these experimental animal models may be more reflective of inflammatory cardiomyopathies in humans rather than ischemic cardiomyopathies, which are the most common etiology of CHF in the adult human population.

4.5.1 Clinical Trial Data

The Anti-TNF α Therapy Against CHF (ATTACH, C0168T30) study is a completed, Phase II study in patients with CHF. A total of 150 patients were enrolled at 32 US study centers between 14 August 2000, and 20 April 2001. The primary objective of the trial was to evaluate, in a preliminary fashion, the effect of Remicade on clinical status at 14 weeks following randomization in patients with stable New York Heart Association (NYHA) Class III or IV CHF resulting from systolic dysfunction. Clinical status was also evaluated at 28 weeks following randomization by a clinical composite score based on death, hospitalization for worsening heart failure, change in NYHA classification, and Patient Global Assessment.

Patients were randomized in approximately equal proportions to placebo, Remicade 5 mg/kg, or Remicade 10 mg/kg, each given as a 2-hour IV infusion at weeks 0, 2, and 6 postrandomization. Remicade infusions did not exceed a maximum of 1 gm. Within the study population, 64.7% of patients (n=97) presented with cardiomyopathies secondary to chronic coronary artery disease while 35.3% (n=53) presented with nonischemic cardiomyopathies. Overall, there were more male patients (85.1% vs. 75.5%) and more African-Americans patients (9.9% vs. 8.2%) in the Remicade cohorts than in the placebo group. Though only trends, patients in the 10 mg/kg Remicade cohort had a higher proportion of African-American patients (13.7% vs. 8.2%), higher rates of ischemic cardiomyopathy (70.6% vs. 63.3%), and greater numbers of patients in NYHA Class IV CHF (7.8% vs. 4.1%) at presentation compared with those who received placebo.

The 14-week data showed no significant difference overall in clinical status (as defined above) in Remicade-treated patients and a trend towards increased incidence of hospitalization for worsening heart failure in patients treated at the higher Remicade dose of 10 mg/kg. There were no differences in rates of death (0% in both), combined death/hospitalization (4.0% vs. 4.2%), or any hospitalization (10% vs. 12.2%) in the Remicade 5 mg/kg-treated patients when compared with placebo-treated patients. There was a statistically significant increase in left ventricular ejection fraction from baseline (3.5% vs. 0%, p=0.013) in the 5-mg/kg Remicade cohort and for the two Remicade

cohorts combined (2.0% vs. 0%, $p=0.039$) compared with that in the placebo cohort. At 14 weeks, patients who received either dose of Remicade in this study had no increased incidence of upper respiratory infections (8.9% vs. 14.6%), arrhythmias (11.9% vs. 12.5%), pneumonia (3.0% vs. 2.1%), or infections (23.8% vs. 33.3%) compared with placebo.

There were 7 deaths reported during this study: 1 occurred prior to week 14 in the 10 mg/kg Remicade group and 6 after week 14 (2 in the 5 mg/kg Remicade group and 4 in the 10-mg/kg Remicade group). All deaths occurred in male patients with the primary diagnosis of ischemic cardiomyopathy. In follow-up at 1 year, 8 patients in the 10-mg/kg Remicade group died compared with 4 patients each in the placebo and 5-mg/kg Remicade groups. At 28 weeks, 14 of 101 patients (14%) in the Remicade groups (3 at 5 mg/kg and 11 at 10 mg/kg) had been hospitalized for worsening heart failure compared with 5 of the 49 patients in the placebo group (10%).

In this small pilot trial, Remicade doses of 5 and 10 mg/kg did not improve clinical status in patients with stable Class III/IV heart failure resulting from systolic dysfunction. In addition, there was a non-significant trend towards more deaths with higher doses of Remicade. Because of this small Phase II study, it was recommended that doses greater than 5 mg/kg not be administered to patients with CHF. Remicade should be used with caution in patients with mild heart failure (NYHA Class I/II). Patients should be closely monitored and Remicade must not be continued in patients who develop new or worsening symptoms of heart failure.

4.5.2 Labeling

4.5.2.1.1 CONTRAINDICATIONS

Remicade is contraindicated in patients with moderate or severe (NYHA Class III/IV) congestive heart failure (see WARNINGS, Congestive Heart Failure).

4.5.2.1.2 Warnings Section:

Congestive Heart Failure

Doses greater than 5 mg/kg should not be administered to patients with congestive heart failure (CHF). Remicade should be used with caution in patients with mild heart failure (NYHA Class I/II). Patients should be closely monitored, and Remicade must not be continued in patients who develop new or worsening symptoms of heart failure (see CONTRAINDICATIONS and ADVERSE REACTIONS, Congestive Heart Failure).

4.5.2.1.3 Adverse Reactions:

Congestive Heart Failure

In a phase II study evaluating Remicade in NYHA Class III/IV CHF patients (left ventricular ejection fraction $\leq 35\%$), higher incidences of mortality and hospitalization

due to worsening heart failure were seen in Remicade-treated patients, especially those treated with 10 mg/kg. One hundred and fifty patients were treated with 3 infusions of Remicade 5 mg/kg, 10 mg/kg, or placebo over 6 weeks. At 28 weeks, 4 of 101 patients treated with Remicade (1 at 5 mg/kg and 3 at 10 mg/kg) died compared with no deaths among the 49 placebo-treated patients. In follow-up, at 38 weeks, 9 patients treated with Remicade (2 at 5 mg/kg and 7 at 10 mg/kg) died compared with one death among the placebo-treated patients. At 28 weeks, 14 of 101 patients treated with Remicade (3 at 5 mg/kg and 11 at 10 mg/kg) were hospitalized for worsening CHF compared with 5 of the 49 placebo-treated patients (see CONTRAINDICATIONS and WARNINGS, Congestive Heart Failure).

5.0 Summary and Conclusions

5.1 Benefits/Risks

5.1.1 Benefits

The efficacy of Remicade was evaluated in patients with RA in four placebo-controlled trials and two open-label trials. In patients with an inadequate response to MTX, Remicade, in combination with MTX, has been shown to rapidly relieve the signs and symptoms of RA, to inhibit the progression of structural damage and to improve physical function in patients with active RA. Placebo controlled data through 102 weeks in ATTRACT trial (T22) formed the basis for FDA's approval in the improvement in physical function, thereby fulfilling an important unmet medical need.

The efficacy of Remicade for active RA in patients, who have had an inadequate response to methotrexate, was clearly demonstrated in clinical trials, specifically:

- Remicade provided a consistent, durable, clinically meaningful and statistically significant benefit by inhibiting the progression of structural damage, with regard to both erosions and joint space narrowing.
- Remicade provided a consistent, durable, clinically and statistically significant benefit by reducing the signs and symptoms of RA. Remicade also provided a major clinical response (i.e., an ACR 70% response for 6 consecutive months) in a significantly greater proportion of patients than with placebo.
- Remicade has also demonstrated a consistent, durable, clinically meaningful and statistically significant benefit by improving physical function, fulfilling an unmet medical need. Remicade is the first and only anti-rheumatic drug or biologic approved for this indication.

In Crohn's disease, as is currently indicated, Remicade has been shown to rapidly reduce signs and symptoms and induce and maintain clinical remission in patients in moderately to severely active disease, and effectively reduce the number of draining enterocutaneous fistulas in patients with fistulizing disease. The efficacy of Remicade in Crohn's disease has been clearly demonstrated in clinical trials, specifically:

- Remicade reduced clinical signs and symptoms, induced and maintained clinical remission in patients with active Crohn's disease who are not responding to corticosteroid therapy, a benefit for which no other therapy is indicated.
- Remicade has been shown to allow Crohn's disease patients to have their corticosteroid therapy reduced or withdrawn, while achieving greater efficacy.

- Remicade has provided significant improvement in the disease specific inflammatory bowel disease questionnaire (IBDQ), particularly the bowel and systemic components, and in the physical component summary score of the general health-related quality of life questionnaire SF-36.
- Remicade has been shown to result in endoscopic evidence of mucosal healing in patients with mucosal ulceration at baseline in an endoscopy sub-study.

5.1.2 Risk

The safety of Remicade has been assessed in 15 completed clinical trials, as well as a number of ongoing studies. In addition, information from postmarketing surveillance on greater than 365,000 patients world-wide treated with Remicade has been analyzed. Several risks have been consistently identified and other areas of concern are noted as a result of information available from other anti-TNF agents.

- Infections, including TB and other opportunistic infections and sepsis, have been observed with Remicade therapy, although in clinical studies, serious infections were not more frequent in Remicade-treated patients than in patients who received placebo.
- Remicade therapy has been associated in rare cases with neurological events such as optic neuritis, seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis.
- Acute infusion reactions (including anaphylaxis) and delayed hypersensitivity (serum sickness-like) reactions have been observed with Remicade infusions, although serious infusion reactions were uncommon in clinical trials and during postmarketing surveillance.
- Treatment with Remicade may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome.
- Malignancies, including lymphoma, have been observed in clinical trials with Remicade. Since patients with long duration and severity of rheumatoid arthritis or Crohn's disease plus chronic exposure to immunosuppressant therapies are more prone to develop lymphoma, currently there are insufficient data to determine whether Remicade contributed to the development of these events. For non-LPD malignancies, the observed rates and incidences were similar to those expected in the general population. These adverse events will continue to be monitored.

5.2 Conclusions

Given the serious, chronic and debilitating nature of rheumatoid arthritis and Crohn's disease and the demonstrated clinical benefit of Remicade in these conditions, it is widely recognized that Remicade has set a new therapeutic standard in patients who have had an inadequate response to conventional therapy.

Clinical trial, and in particular, postmarketing data indicate an increased risk for reactivation of latent TB with Remicade therapy. This risk is recognized and reflected in the current labeling for the product. Centocor has undertaken a multi-faceted approach to communicate the risks of developing TB while on Remicade, as well as guidelines for tuberculin skin testing and treatment of latent TB infection. The communication plan includes ongoing education programs for health care providers and patients, and includes measures to assess the effectiveness of the communication. The results of the follow-up study indicate that the US education program was successful in having physicians perform skin tests for latent TB and to initiate anti-TB therapy, when necessary, before starting patients on Remicade. Importantly, the high percentage of patients being tested for TB prior to receiving Remicade coincides with a continuous decline in the number of spontaneous reports of active TB in the US over the past 12 months.

The association between Remicade and opportunistic infections is more difficult to assess since the event rates are lower, and patients typically taking Remicade have other risk factors for such infections (for example, concomitant immunosuppressive therapies); however, Centocor currently has ongoing studies to better characterize these risks.

In considering any possible increased risk of lymphoproliferative disease (LPD) in patients treated with Remicade, it is essential to be aware of the higher incidence of such disorders in patients with rheumatoid arthritis and Crohn's disease than in the general population, and, for RA in particular, the previously reported association between disease severity, prior immunosuppressive therapy and LPD risk. Thus, although the incidence of LPD reported in Remicade clinical trials exceeds that of an age, gender, and race-adjusted general population (the SEER database), the rates compare favorably with other RA cohorts included in a like-for-like comparison (the National Database Registry). Furthermore, there are indications from Centocor's own clinical trial population that it is disease severity and other linked characteristics (disease duration, functional score, etc.) that is most strongly associated with LPD risk, rather than Remicade use. Any comparisons of LPD risk between different anti-TNF agents must therefore take baseline patient characteristics into account.

Although it is not yet possible to reach a definitive conclusion regarding a possible link between LPD and Remicade therapy, Centocor continues to examine the issue in clinical trials, through post-marketing pharmacovigilance, and in large RA and CD disease registries. For non-LPD malignancies, the observed rates and incidences were similar to those expected in the general population. However, these adverse events will also continue to be monitored.

With the availability of three anti-TNF agents in the US and the opportunity for increased knowledge and understanding, Centocor looks forward to the Arthritis Advisory Committee and the FDA's deliberations, assessment and guidance on the potential risk of anti-TNF agents in malignancies and lymphoproliferative disease.

6.0 Bibliography

Bachman TR, Sawitzke AD, Perkins SL, Ward JH, Cannon GW. Methotrexate-associated lymphoma in patients with rheumatoid arthritis. *Arthritis & Rheum* 1996;39:325-329.

Baecklund E, Ekbom A, Sparén P, Feltelius N, Klareskog L. Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case-control study. *BMJ* 1998;317:180-181.

Bernstein CN, Blanchard JF, Kliever E, Wajda A. Cancer risk in patients with inflammatory bowel disease: a population-based study. *Cancer* 2001;91:854-862.

Brown LS, Greene MH, Gershon SK, Edwards ET, Braun MM. Tumor necrosis factor antagonist therapy and lymphoma development. *Arthritis & Rheum* 2002;46:3151-3158.

Bryant D, Becker L, Richardson J, et al. Cardiac failure in transgenic mice with myocardial expression of tumor necrosis factor- α . *Circulation* 1998;97:1375-1381.

Dawson TM, Starkebaum G, Wood BL, Willkens RF, Gown AM. Epstein-Barr virus, methotrexate, and lymphoma in patients with rheumatoid arthritis and primary sjögren's syndrome: case series. *J Rheum* 2001;28:47-53.

DeVita VT Jr, Hellman S, Rosenberg SA. *Cancer: Principles and Practice of Oncology*. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001.

Ellman MH, Hurwitz H, Thomas C, Kozloff M. Lymphoma developing in a patient with rheumatoid arthritis taking low dose weekly methotrexate. *J Rheum* 1991;18:1741-1743.

Georgescu L, Quinn GC, Schwartzman S, Paget SA. Lymphoma in patients with rheumatoid arthritis: association with the disease state or methotrexate treatment. *Sem Arthritis Rheum* 1997;26:794-804.

Gridley G, McLaughlin JK, Ekbom A, et al. Incidence of cancer among patients with rheumatoid arthritis. *J Natl Cancer Inst* 1993;85:307-311.

Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;359:1541-1549.

Isomaki H, Hakulinen T, Joutsenlahti U. Excess risk of lymphoma, leukemia and myeloma in patients with rheumatoid arthritis. *Ann Rheum Dis* 1982;41 (suppl):34.

Jones M, Symmons D, Finn J, Wolfe F. Does exposure to immunosuppressive therapy increase the 10-year malignancy and mortality risks in RA? Matched cohort study. *Br J Rheum* 1996;35:738-745.

Kamel OW, van de Rijn M, Weiss LM, et al. Brief report: reversible lymphomas associated with Epstein-Barr virus occurring during methotrexate therapy for rheumatoid arthritis and dermatomyositis. *NEJM* 1993;328:1317-1321.

Katusic S, Beard CM, Kurland LT, Weis JW, Bergstralh E. Occurrence of malignant neoplasms in the Rochester, Minnesota, rheumatoid arthritis cohort. *The American Journal of Medicine* 1985;78(suppl 1A):50-55.

Kingsmore SF, Hall BD, Allen NB, Rice JR, Caldwell DS. Association of methotrexate, rheumatoid arthritis and lymphoma: report of 2 cases and literature review. *J Rheumatol* 1992;19:1462-1465.

Kubota T, McTiernan CF, Frye CS, et al. Dilated cardiomyopathy in transgenic mice with cardiac-specific overexpression of tumor necrosis factor- α . *Circulation Research* 1997;81:627-635.

Lipsky PE, van der Heijde D, St. Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. *NEJM* 2000;343:1594-1602.

Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor α monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis & Rheum* 1998;41:1552-1563.

Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumor necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. *Lancet* 1999;354:1932-1939.

Mariette X, Cazals-Hatem D, Warszawski J, et al. Lymphomas in rheumatoid arthritis patients treated with methotrexate: a 3-year prospective study in France. *Blood* 2002;99:3909-3915.

Mellemkjaer L, Linet MS, Gridley G, Frisch M, Moller H, Olsen JH. Rheumatoid arthritis and cancer risk. *Eur J Cancer* 1996;32A:1753-1757.

Moritomo H, Ueda T, Hiyama T, Hosono N, Mori S, Komatsubara Y. The risk of cancer in rheumatoid patients in Japan. *Scand J Rheumatol* 1995;24:157-159.

Periodic safety update report for infliximab: 24 February 2002 – 23 August 2002. Spring House, PA: Johnson and Johnson Pharmaceutical Research and Development; 17 October 2002.

Prior P. Cancer and rheumatoid arthritis: epidemiologic considerations. *The American Journal of Medicine* 1985;78(suppl 1A):15-21.

Salloum E, Cooper DL, Howe G, et al. Spontaneous regression of lymphoproliferative disorders in patients treated with methotrexate for rheumatoid arthritis and other rheumatic diseases. *J Clin Oncol* 1996;14:1943-1949.

Stewart M, Malkovska V, Krishnan J, Lessin L, Barth W. Lymphoma in a patient with rheumatoid arthritis receiving methotrexate treatment: successful treatment with rituximab. *Ann Rheum Dis* 2001;60:892-893.

Symmons DP. Neoplasia in rheumatoid arthritis. *J Rheumatol* 1988;15:1319-1322.

Symmons DP, Ahem M, Bacon PA, et al. Lymphoproliferative malignancy in rheumatoid arthritis: a study of 20 cases. *Ann Rheum Dis* 1984;43:132-135.

Taillan B, Garnier G, Castanet J, Ferrari E, Pesce A, Dujardin P. Lymphoma developing in patient with rheumatoid arthritis taking methotrexate. *Clinical Rheumatology* 1993;12:93-94.

Yokoyama T, Vaca L, Rossen RD, Durante W, Hazarika P, Mann DL. Cellular basis for the negative inotropic effects of tumor necrosis factor- α in the adult mammalian heart. *J Clin Invest* 1993;92:2303-2312.

Appendix A Calculation of Standard Incidence Ratios

Calculation of SIRs

Calculation of Expected Number of Cancer Cases

The expected number of cancer cases in the general US population, according to the NIH SEER database, is the number of cases expected in a cohort of individuals that is similar (with respect to age, gender, and duration of follow-up) to those patients enrolled in Remicade clinical trials. Centocor uses the 1999 SEER database (Surveillance, Epidemiology and End Results), adjusted for age and gender.

The SEER database summarizes cancer data by gender and age groups (in 5 year groups, e.g., 30-34 years of age). The SEER rate of malignancy is calculated as the number of cancer cases reported in an age-gender group, divided by the number of people represented in the database in that age-gender group.

The expected number of cancer cases in the general US population in each age-gender group is calculated as the SEER rate of malignancy, multiplied by the number of patient years of follow-up in that age-gender category from the Remicade database. The expected number of cancer cases provided in Centocor ISS tables is the sum of all expected numbers of cancer cases for all age-gender groups.

Calculation of Standardized Incidence Ratio (SIR) and Confidence Interval

The Standard Incidence Ratio (SIR) is calculated as

$$SIR = \frac{\text{observed cases}}{\text{age-gender-race adjusted incidence in the general US population from SEER}}.$$

An exact 95% confidence interval for the SIR is calculated based on Poisson distribution. The two confidence limits are computed as

$$CI_L: \quad SIR \times \lambda_L / D \text{ where } \lambda_L \text{ is the solution of } \sum_{i=D}^{\infty} \frac{e^{-\lambda_L} \lambda_L^i}{i!} = 0.025$$

$$\text{and } CI_U: \quad SIR \times \lambda_U / D \text{ where } \lambda_U \text{ is the solution of } \sum_{i=0}^D \frac{e^{-\lambda_U} \lambda_U^i}{i!} = 0.025$$

and D=number of observed cases.

References:

Sahai, H and Khurshid, A (1996). *Statistics in Epidemiology. Methods, Techniques, and Applications*. CRC Press. Boca Raton.
 A software, PAMCOMP (Ref: <http://medweb.unimuenster.de/institute/epi/pamcomp/pamcomp.html>) Dirk Taeger, Yi Sun, Ulrich Keil, Kurt Straif: A Standalone Windows Application for Computing Exact Person-Years, Standardized Mortality Ratios and Confidence Intervals in Epidemiological Studies, *Epidemiology* 2000; 11: 607-608.
 was used to generate these exact confidence intervals. The accuracy of this software was verified using the numbers in various publications.

Appendix B Listing of Lymphomas Reported Cumulatively by Indication and Adverse Event Term

APPENDIX B Listing of Lymphomas Reported Cumulatively by Indication and Adverse Event Term

MFR Number	Country	Age	Gender	Indication	Verbatim	AE Terms	AE Outcome
NSADSS2002009011	FRA	62	M	Celiac Sprue	Cutaneous T Cell Lymphoma	Lymphoma Malignant	Unk
NSADSS2000003308	SWE	26	M	Crohn's Disease	Lymphoma	Lymphoma Malignant	Unk
NSADSS2001001360	USA	34	F	Crohn's Disease	Large Cell Lymphoma	Lymphoma Malignant	Unk
NSADSS2001024850	USA	32	F	Crohn's Disease	Lymphoma of Small Bowel	Lymphoma Malignant	Death
NSADSS2001030744	ITA	42	M	Crohn's Disease	B Cell Lymphoma	Lymphoma Malignant	Recovered
NSADSS2001036603	SWE	23	F	Crohn's Disease	Lymphoma	Lymphoma Malignant	Improved
NSADSS2001036604	SWE	77	M	Crohn's Disease	Lymphoma	Lymphoma Malignant	Death
NSADSS2002005414	AUS	33	M	Crohn's Disease	Anaplastic Intestinal Lymphoma	Lymphoma Malignant	Death
NSADSS2002012080	USA	Unk	F	Crohn's Disease	Lymphoma	Lymphoma Malignant	Death
NSADSS2002018092	USA	18	M	Crohn's Disease	Lymphoma	Lymphoma Malignant	Unk
NSADSS2002018268	GBR	Unk	Unk	Crohn's Disease	Anaplastic Lymphoma	Lymphoma Malignant	Unk
NSADSS2002025924	USA	73	F	Crohn's Disease	Malignant Lymphoma	Lymphoma Malignant	Unk
NSADSS2002025927	USA	26	M	Crohn's Disease	Hodgkin's Lymphoma	Lymphoma Malignant	Unk
SP-200001802	USA	Unk	F	Crohn's Disease	Intra-Abdominal Lymphoma	Lymphoma Malignant	Unk
NSADSS2002009296	FIN	48	M	Crohn's Disease	Lymphoma	Lymphoma-Like Disorder	Unk
SP-199900160	USA	29	M	Crohn's Disease	Hodgkin's Lymphoma	Lymphoma-Like Disorder	Unk
SP-200002076	GBR	Unk	F	Crohn's Disease	Lymphoma	Lymphoma-Like Disorder	Unk
C1-199800224	GBR	Unk	M	Crohn's Disease	B Cell Follicular Lymphoma	Non-Hodgkin's Lymphoma	Unk
NSADSS2002025716	USA	31	M	Crohn's Disease	T-Delta Gamma Lymphoma	Non-Hodgkin's Lymphoma	Unchanged
SP-200002111	USA	74	F	Crohn's Disease	B Cell Non-Hodgkin's Lymphoma	Non-Hodgkin's Lymphoma	Unk
SP-200002121	USA	62	M	Crohn's Disease	Non-Hodgkin's Lymphoma	Non-Hodgkin's Lymphoma	Death
NSADSS2001032091	GBR	Unk	F	Dermatomyositis	Lymphoma	Lymphoma Malignant	Unk
NSADSS2002014920	USA	29	M	Graft-Versus-Host Disease	Stage III-A Nodular Sclerosing Hodgkin's Disease	Lymphoma Malignant	Death
NSADSS2001007022	POR	70	F	Rheumatoid Arthritis	Lymphoma of the Brain	Brain Neoplasm Malignant	Death
NSADSS2001001276	CAN	67	F	Rheumatoid Arthritis	Follicular Mixed Lymphoma	Lymphoma Malignant	Unk
NSADSS2001004267	USA	83	M	Rheumatoid Arthritis	B Cell Lymphoma	Lymphoma Malignant	Death
NSADSS2001006776	USA	49	M	Rheumatoid Arthritis	B Cell Lymphoma	Lymphoma Malignant	Unchanged
NSADSS2001018631	USA	59	M	Rheumatoid Arthritis	Stage III-A Nodular Sclerosing Hodgkin's Disease	Lymphoma Malignant	Unk

Key: AUS = Austria; BEL = Belgium; CAN = Canada; F = female; FIN = Finland; FRA = France; GBR = Great Britain; ITA = Italy; M = male; POR = Portugal; SWE = Sweden; Unk = unknown

(continued)

Appendix B Listing of Lymphomas Reported Cumulatively by Indication and Adverse Event Term (continued)

MFR Number	Country	Age	Gender	Indication	Verbatim	AE Terms	AE Outcome
NSADSS2001018840	USA	66	M	Rheumatoid Arthritis	Hodgkin's Lymphoma	Lymphoma Malignant	Death
NSADSS2001019237	USA	61	F	Rheumatoid Arthritis	Malignant Lymphoma	Lymphoma Malignant	Unk
NSADSS2001020244	USA	67	M	Rheumatoid Arthritis	B Cell Lymphoma	Lymphoma Malignant	Unk
NSADSS2001021671	USA	Unk	F	Rheumatoid Arthritis	Low Grade Lymphoma and Sjogren's Syndrome	Lymphoma Malignant	Unk
NSADSS2001023504	USA	68	M	Rheumatoid Arthritis	Lymphoma	Lymphoma Malignant	Unk
NSADSS2001027484	USA	78	F	Rheumatoid Arthritis	Lymphoma	Lymphoma Malignant	Unk
NSADSS2001029222	USA	68	F	Rheumatoid Arthritis	Probable Lymphoma	Lymphoma Malignant	Unk
NSADSS2001031746	USA	Unk	F	Rheumatoid Arthritis	Low Grade Lymphoma	Lymphoma Malignant	Unk
NSADSS2001034170	GBR	68	F	Rheumatoid Arthritis	Large B Cell Lymphoma	Lymphoma Malignant	Unk
NSADSS2002000247	CAN	72	F	Rheumatoid Arthritis	Follicular Mixed Lymphoma	Lymphoma Malignant	Unk
NSADSS2002002393	USA	Unk	M	Rheumatoid Arthritis	Lymphoma	Lymphoma Malignant	Unk
NSADSS2002002621	USA	68	F	Rheumatoid Arthritis	Low Grade Lymphoma	Lymphoma Malignant	Unk
NSADSS2002006110	FRA	50	M	Rheumatoid Arthritis	Hodgkin's Disease	Lymphoma Malignant	Unk
NSADSS2002008807	USA	56	F	Rheumatoid Arthritis	Hodgkin's Lymphoma	Lymphoma Malignant	Unk
NSADSS2002014086	BEL	37	F	Rheumatoid Arthritis	T Cell Lymphoma	Lymphoma Malignant	Unk
NSADSS2002015884	SWE	58	F	Rheumatoid Arthritis	Malignant Lymphoma of B Cell Type	Lymphoma Malignant	Unk
NSADSS2002017408	USA	81	F	Rheumatoid Arthritis	Lymphoma	Lymphoma Malignant	Unchanged
NSADSS2002017964	USA	58	M	Rheumatoid Arthritis	Hodgkin's Lymphoma	Lymphoma Malignant	Unk
NSADSS2002018501	CAN	64	M	Rheumatoid Arthritis	Follicular Lymphoma	Lymphoma Malignant	Unk
NSADSS2002018694	USA	69	F	Rheumatoid Arthritis	Large Cell Lymphoma	Lymphoma Malignant	Unk
NSADSS2002022016	USA	Unk	M	Rheumatoid Arthritis	Lymphoma	Lymphoma Malignant	Unk
NSADSS2002023534	USA	65	F	Rheumatoid Arthritis	Cutaneous T Cell Lymphoma	Lymphoma Malignant	Unk
NSADSS2002026357	USA	52	M	Rheumatoid Arthritis	Lymphoma	Lymphoma Malignant	Death
NSADSS2002027306	USA	71	F	Rheumatoid Arthritis	Hodgkin's Lymphoma	Lymphoma Malignant	Unk
NSADSS2002027877	USA	64	F	Rheumatoid Arthritis	Low Grade B Cell Lymphoma	Lymphoma Malignant	Unk
SP-200001624	USA	77	M	Rheumatoid Arthritis	Burkett's Lymphoma	Lymphoma Malignant	Unk
SP-200000531	USA	70	M	Rheumatoid Arthritis	Large Cell Lymphoma	Lymphoma-Like Disorder	Unk
SP-200002117	USA	61	M	Rheumatoid Arthritis	Hodgkin's Disease	Lymphoma-Like Disorder	Unk
NSADSS2001004213	USA	70	M	Rheumatoid Arthritis	Non-Hodgkin's Lymphoma	Non-Hodgkin's Lymphoma	Death
NSADSS2001005273	CAN	57	F	Rheumatoid Arthritis	Centro-Follicular B Cell Lymphoma	Non-Hodgkin's Lymphoma	Unk

Key: AUS = Austria; BEL = Belgium; CAN = Canada; F = female; FIN = Finland; FRA = France; GBR = Great Britain; ITA = Italy; M = male; POR = Portugal; SWE = Sweden; Unk = unknown

(continued)

Appendix B Listing of Lymphomas Reported Cumulatively by Indication and Adverse Event Term (continued)

NSADSS2001006724	USA	68	F	Rheumatoid Arthritis	Malignant Non-Hodgkin's Lymphoma	Non-Hodgkin's Lymphoma	Unchanged
NSADSS2001006842	BEL	76	F	Rheumatoid Arthritis	Non-Hodgkin's Lymphoma	Non-Hodgkin's Lymphoma	Unk
NSADSS2001009438	USA	68	M	Rheumatoid Arthritis	Non-Hodgkin's Lymphoma	Non-Hodgkin's Lymphoma	Unk
NSADSS2002001266	USA	49	F	Rheumatoid Arthritis	B Cell Lymphoma	Non-Hodgkin's Lymphoma	Unk
NSADSS2002002450	USA	80	M	Rheumatoid Arthritis	B Cell Lymphoma	Non-Hodgkin's Lymphoma	Unk
NSADSS2002003176	USA	49	F	Rheumatoid Arthritis	B Cell Lymphoma	Non-Hodgkin's Lymphoma	Unk
NSADSS2002005871	ITA	64	M	Rheumatoid Arthritis	Non-Hodgkin's Lymphoma	Non-Hodgkin's Lymphoma	Improved
NSADSS2002010584	USA	84	F	Rheumatoid Arthritis	Non-Hodgkin's Lymphoma	Non-Hodgkin's Lymphoma	Unk
PRIUSA2000012416	USA	68	F	Rheumatoid Arthritis	Non-Hodgkin's Lymphoma	Non-Hodgkin's Lymphoma	Unk
SP-200002129	USA	48	M	Rheumatoid Arthritis	B Cell Non Hodgkins Lymphoma	Non-Hodgkin's Lymphoma	Unk
NSADSS2002004992	USA	Unk	Unk	Unknown	Lymphoma	Lymphoma Malignant	Unk
NSADSS2002020279	CAN	Unk	Unk	Unknown	Lymphoma	Lymphoma Malignant	Unk
NSADSS2002008898	GBR	56	M	Wegener's Granulomatosis	Lymphoma	Non-Hodgkin's Lymphoma	Unk

Key: AUS = Austria; BEL = Belgium; CAN = Canada; F = female; FIN = Finland; FRA = France; GBR = Great Britain; ITA = Italy; M = male; POR = Portugal; SWE = Sweden; Unk = unknown

(continued)