DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

February 24, 2003

Dear Advisors:

Regarding the FDA briefing document for March 4 (Safety Update on TNFs), this mailing contains:

- Legible copies of figure 1 and tables 12-15. Please insert the corrected pages into your briefing document and accept my apologies for the poor quality of the initial mail out.
- Erratum to correct minor errors noted in the medical reviews contained in appendices D and E
- Questions for which FDA seeks your advice.

I look forward to this upcoming advisory meeting.

Sincerely,

Karen Weiss

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Components of ACR Response

Parameter (median)	Study II				Study III			
	Placebo N=110		HUMIRA[a] N=113		Placebo/MTX N=200		HUMIRA[a]/MTX N=207	
	Baseline	Wk 26	Baseline	Wk 26	Baseline	Wk 24	Baseline	Wk 24
Number of tender joints (0-68)	35	26	31	16*	26	15	24	8*
Number of swollen joints (0-66)	19	16	18	10*	17	11	18	5*
Physician global assessment[b]	7.0	6.1	6.6	3.7*	6.3	3.5	6.5	2.0*
Patient global assessment[b]	7.5	6.3	7.5	4.5*	5.4	3.9	5.2	2.0*
Pain[b]	7.3	6.1	7.3	4.1*	6.0	3.8	5.8	2.1*
Disability index (HAQ)[c]	2.0	1.9	1.9	1.5*	1.5	1.3	1.5	0.8*
CRP (mg/dL)	3.9	4.3	4.6	1.8*	1.0	0.9	1.0	0.4*

[a] 40 mg HUMIRA administered every other week

[b] Visual analogue scale; 0 = best, 10 = worst

[c] Disability Index of the Health Assessment Questionnaire[2]; 0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity

* $p<0.001$, HUMIRA vs. placebo, based on mean change from baseline

The time course of ACR 20 response for Study III is shown in figure 1.

In Study III, 85% of patients with ACR 20 responses at week 24 maintained the response at 52 weeks. The time course of ACR 20 response for Study I and Study II were similar.

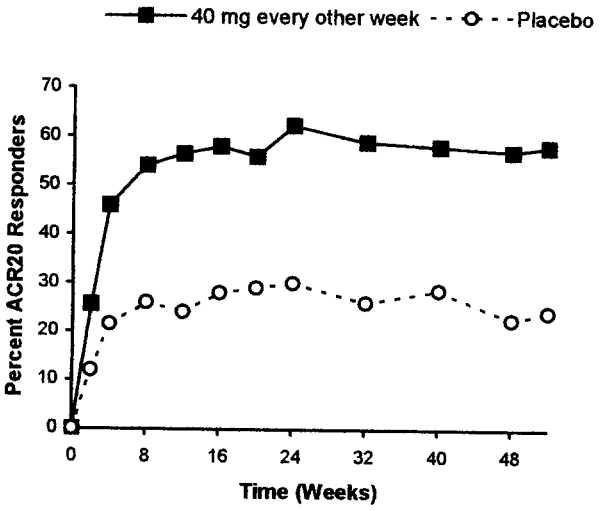

Figure 1: Study III ACR 20 Responses over 52 Weeks

In Study III, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and Joint Space Narrowing (JSN) score, at month 12 compared to baseline. At baseline, the median TSS was approximately 55 in the placebo and 40 mg every other week groups. The results are shown in Table 3. HUMIRA/MTX treated patients demonstrated less radiographic progression than patients receiving MTX alone.

2. *Etanercept*

Safety and efficacy data were recently reviewed by the agency for patients treated with etanercept in long-term open-label clinical trials for three years. As shown in Table 12, 546 patients have received etanercept for at least 3 years and 427 for 4 years. A total of 14 deaths were observed in the clinical trials safety database. Of these, 5 (36%) were cardiovascular in nature, 4 (29%) were related to malignancies, 2 (14%) were infectious, 1 (7%) was pulmonary and 2 (14%) were unclassified (Table 13). Since there is no concurrent control group, historical data were obtained from the Olmsted County database of RA patients for comparison. As shown in Table 14, the percent of patients dying of cardiovascular, infectious and pulmonary causes were similar. A lower proportion of deaths were related to malignancies in the Olmsted County database (10%) than in the etanercept database (29%).

To determine how the number of deaths observed in the etanercept database compared with the number expected for a group of adults in the general population, the expected number of deaths was calculated using the National Vital Statistics Report (Kochanek, 2001) adjusting for age and sex (Table 15). For all adults in the database, as well as for adults participating in the MTX combination trial and for the children with JRA, the observed number of deaths was lower than the expected rate. No trends were seen to indicate an increase in the death rate with longer exposure to etanercept.

Table 12: Duration of treatment of patients being following in etanercept long-term safety studies

	Adults			Pediatric Patients (n = 69)	All Etanercept (n = 782)
	Total Adults (n = 713)	Adults w/o 16.14 (n = 628)	16.14 (n = 85)		
Mean duration of dosing period (days)	932	926	975	824	922
Number (%) of patients who received etanercept during:					
Year 1 (0 – 365 days)	713 (100)	628 (100)	85 (100)	69 (100)	782 (100)
Year 2 (366 – 730 days)	553 (78)	479 (76)	74 (87)	52 (75)	605 (77)
Year 3 (731 – 1095 days)	498 (70)	430 (68)	68 (80)	48 (70)	546 (70)
Year 4 (1096 – 1460 days)	403 (57)	358 (57)	45 (53)	24 (35)	427 (55)
Year 5 (1461 – 1825 days)	71 (10)	71 (11)	0 (0)	0 (0)	71 (9)

Table 13: Deaths occurring among all adults in the long-term database

Study of Occurrence/ Pt. No.	Age/ Sex	Day of Death	Days on Etanercept	Event
016.0008/0003	69/M	200	199	Myocardial infarction
016.0018/0314	60/F	853	853	Cardiac arrest
016.0018/0336	73/F	770	717	Myocardial infarction
016.0018/0407	60/F	977	977	Respiratory failure
016.0018/0450	62/F	1015	996	Fever of unknown origin
016.0018/0620	76/F	1365	1334	Acute cardiac arrest/ myocardial infarction
016.0018/1137	67/F	513	509	Cardiac arrest
016.0018/1228	57/M	482	481	Cardiac arrest secondary to biliary cancer
016.0018/1492	78/F	451	447	Lung cancer
016.0018/1562	52/F	353	342	Septicemia
016.0018/1571	43/F	1059	1048	Lung cancer
016.0018/1631	62/F	404	383	Injury accident
016.0018/1702	57/M	697	685	Post-operative retroperitoneal hematoma
016.0019/0110	57/F	126	106	Ovarian cancer

Table 14: Mortality in the etanercept long-term database compared to population-based database

Cause of death	Etanercept long-term database 14 deaths / 1819 patient-years	Olmsted County MN database 279 deaths / 6350 patient-years
Cardiovascular	36%	39%
Malignancy	29%	10%
Infectious	14%	15%
Pulmonary	7%	11%
Cerebrovascular	0%	9%
Other	14%	16%

TAB D: Etancercept/CHF Medical Review – Erratum

Page 28, under conclusions, the review document should state that, in terms of labeling, when all of the results are considered together, the level of concern probably rises to that of a *precaution*. (emphasis added)

Tab E: Infliximab /CHF Medical Review

Page 8 – corrected Table 4 (corrections for "digoxin")

Table 4: Concomitant Medication Use

	Placebo n=49	Infliximab 5 mg/kg n=50	Infliximab 10 mg/kg n=51	Total n = 150
digoxin	37 (75.5)	40 (80)	40 (78.4)	117 (78)
diuretics	46 (93.9)	49 (98)	50 (98)	145 (96.7)
loop	41 (83.7)	44 (88)	47 (92.2)	132 (88)
aldosterone antagonist	18 (36.7)	23 (46)	17 (33.3)	58 (38.7)
other	12 (24.5)	9 (18)	13 (25.5)	34 (22.7)
beta-blockers	37 (75.5)	32 (64)	41 (80.4)	110 (73.3)
ACE inhibitors	41 (83.7)	40 (80)	41 (80.4)	122 (81.3)
angiotensin II antagonists	12 (24.5)	14 (28)	12 (23.5)	38 (25.3)
calcium channel blockers	7 (14.3)	4 (8)	2 (3.9)	13 (8.7)
nitrates	12 (24.5)	19 (38)	21 (41.2)	52 (34.7)
other vasodilators	2 (4.1)	2 (4)	2 (3.9)	6 (4)
anticoagulant	20 (40.8)	22 (44)	25 (49)	67 (44.7)

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Safety: Serious Adverse Events

Through Week 28, cardiac failure was reported as a serious adverse event (SAE) in 22%, 2%, and 8% of subjects in the Infliximab 10 mg/kg, 5 mg/kg, and placebo groups, respectively. Serious adverse events reported in 2 (4%) subjects in the high-dose Infliximab group and in none of the other groups included: increased creatinine phosphokinase, hypotension, myalgia, and myocardial infarction.