ADDENDUM TO THE 14 MAY 2008 BACKGROUND INFORMATION BRIEFING DOCUMENT FOR THE 18 JUNE 2008 DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE (DODAC) MEETING

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2. BACKGROUND

2.1 Updated Information Regarding Cases of Malignancy

An analysis of malignancies in pediatric patients who had received etanercept was presented in Section 7.1 of the 14 May 2008 briefing document. However, case ascertainment continued after preparation of the briefing document, and 4 additional cases of malignancy were subsequently identified. The updated malignancy information is presented in Section 3 of this document.

2.2 Summary of Current and Proposed ENBREL® United States Prescribing Information Label Text

The current Enbrel United States Prescribing Information (USPI) includes a boxed warning for infections including tuberculosis. The current USPI also describes malignancies. Amgen has proposed updated label text for malignancies within the pediatric psoriasis efficacy supplement. Both current USPI and proposed USPI label text for infections, tuberculosis, and malignancies are summarized in Section 4 of this document.

2.3 Bibliography

In addition, this addendum includes a bibliography for all references cited in the 14 May 2008 briefing document, along with a bibliography for the planned core slide deck for Amgen's presentation scheduled for 18 June 2008. The complete bibliography is provided in Section 5 of this document.

3. MALIGNANCY IN PEDIATRIC PATIENTS WHO HAVE RECEIVED ETANERCEPT

3.1 Methodology

To capture all etanercept pediatric case reports of adverse events received by Amgen worldwide through 30 April 2008, a search was conducted of the Amgen Global Safety Adverse Event database (ARISg) for all formulations and dosage forms of etanercept in patients ≤ 22 years of age for cases with adverse events under the *Medical Dictionary for Regulatory Activities* (MedDRA) SOC of "Neoplasms benign, malignant and unspecified (incl cysts and polyps)". The search included worldwide medically confirmed and unconfirmed, serious and non-serious reports, in the safety database where etanercept was identified as a suspect, co-suspect, or suspect-interacting medication. The reports are "all sources" including clinical studies, post-marketing studies, and registry studies; spontaneous reports including those from consumers, health care professionals, literature, other companies and health-authorities; and consumer solicited reports. Generally, adverse events reported in clinical studies are entered in the ARISg database only if they are categorized as serious. Because reports are classified as serious or non-serious at the case level and at the event level, some spontaneous cases may have the designation of serious, while the particular event of interest was not considered serious. All cases were retrieved independently of the reported relationship to causality.

All cases were reviewed to identify those with a reported preferred term indicating malignancy. Then, cases were grouped by age of the patient at diagnoses and age at drug exposure. Cases where the reported terms did not indicate malignancy were excluded from the evaluation, as were reports where etanercept administration was initiated after age 18.

Additionally, on 13 May 2008, Amgen conducted a search of the US Food and Drug Administration (FDA) Spontaneous Report System/Adverse Event Reporting System (SRS/AERS) database for cases of malignancies in patients ≤ 22 years of age that were associated with all formulations and dosage forms of etanercept (Standard MedDRA Query, MedDRA Version 10; data through fourth quarter 2007). The cases suggesting malignancy in this age group were identified, reviewed, and reconciled with ARISg data. As a result, 2 cases were entered in the ARISg database and are included in this summary.

3.2 Results and Analysis

A total of 67 case reports of neoplasia were retrieved through 30 April 2008 using the aforementioned search strategy. Cases with the following preferred terms were not considered as reports of malignancy and, therefore, were not summarized: bladder cyst, breast cyst, cyst, dermal cyst, fibrous histiocytoma, haemorrhagic ovarian cyst, histiocytosis haematophagic, marrow hyperplasia, melanocytic naevus, neoplasm, neoplasm skin, ovarian cyst, ovarian cyst ruptured, skin papilloma, and synovial cyst. In addition, cases where etanercept exposure occurred after the age of 18 were not included according to the search parameters requested by the FDA, with the exception of a single case where etanercept was initiated in a patient aged 18 years and 3 months (Table 2).

The remaining cases were reports that met the FDA requested criteria (ie, where reports of possible malignancy could not be excluded in patients diagnosed before 22 years of age, and etanercept exposure occurred before age 18). A total of 18 cases met the criteria specified in the FDA request. Following medical review, these cases were categorized and presented as tabular summaries:

- 15 cases where a temporal relationship to etanercept exposure exists
  - 9 pediatric cases (etanercept initiated and malignancy onset at < 18 years of age); summarized in Table 1 (7 haematological tumors and 2 other solid tumors)
  - 6 young adult cases (etanercept initiated at < 18 years of age and malignancy onset at ≤ 22 years of age); summarized in Table 2
- 1 case where a malignancy could not be excluded based on the report; summarized in Table 3
- 2 cases where either a malignancy could be excluded (1 case) or was pre-existing (1 case); summarized in Table 4

Of the 18 cases described here, 14 were included in the briefing document prepared for the DODAC meeting (18 June 2008). An additional 4 cases have been included in this document and are summarized in Table 1 (etanercept initiated and malignancy onset at < 18 years of age):

- 2 pediatric cases, 1 case of acute myeloid leukaemia recurrence and 1 case of Hodgkin's disease (lymphoma), were identified from the FDA SRS/AERS database and entered into ARISg on 18 May 2008

- 2 cases of acute lymphocytic leukaemia where the age was listed as “child” rather than by numeric age; the term child was assumed to mean that initiation of etanercept and onset of malignancy occurred at < 18 years of age

Additionally, 5 cases in Table 1 (not including the 4 cases described above), were also included in the response to the FDA request for all pediatric cases (< 18 years old) under the Neoplasms SOC that was submitted to the dermatology division on 07 May 2008. The other cases were not considered as reports of malignancy (see excluded preferred terms at the beginning of this section) and thus are not reported in this document.

Table 1. Pediatric Cases: Patients Treated With Etanercept With Reported Malignancy at < 18 Years of Age

MCN/Country/Source	Adverse Event by Preferred Term	Age at Event (years)	Time From Etanercept Initiation to Onset	Indications	Comments/ Confounders
Hematological					
STX173928 United States/Healthcare professional	leukemia	10	5 months	juvenile arthritis, seronegative arthritis	-
FDA 4719373 US280247[a] United States/Healthcare professional	acute myeloid leukaemia recurrence	12	-	-	not known whether AML preceded etanercept therapy; concomitant infliximab, tacrolimus, mycophenolate
US252341 Germany/ Registry	diffuse large B-cell lymphoma	14	7 years	juvenile arthritis	methotrexate
FDA 5016043 US280246[a] United States/ Healthcare professional	Hodgkin's disease (lymphoma)	15	3.6 years	juvenile arthritis	concomitant methotrexate
QUU263077 United States/ Healthcare professional	lymphoma	17	-	-	report of "possible lymphoma" with insufficient information
US275527[b] DE/Healthcare professional	acute lymphocytic leukaemia	child[c]	approximately 1 year	juvenile arthritis, (Still's syndrome with polyarthritis)	methotrexate

- = not available, AML = acute myeloid leukemia. DE = Germany, MCN = manufacturer control number

[a] Not included in the briefing document prepared for the Dermatologic and Ophthalmologic Drugs Advisory Committee meeting (18 June 2008) or response to FDA request submitted to dermatology division (07 May 2008) because cases were later identified from FDA SRS/AERS database search.

[b] Not included in the briefing document prepared for the Dermatologic and Ophthalmologic Drugs Advisory Committee meeting (18 June 2008) or response to FDA request submitted to dermatology division (07 May 2008).

[c] Age reported as "child" was assumed to mean that initiation of etanercept and onset of malignancy occurred at < 18 years of age.

Table 1. Pediatric Cases: Patients Treated With Etanercept With Reported Malignancy at < 18 Years of Age

MCN/Country/Source	Adverse Event by Preferred Term	Age at Event (years)	Time From Etanercept Initiation to Onset	Indications	Comments/ Confounders
US275768[b] DE/Healthcare professional	acute lymphocytic leukaemia	child[c]	report of "a few months"	polyarthritis	methotrexate
Solid tumors					
US210340 Germany/ Registry	yolk sac tumor site unspecified	16	29 days	juvenile arthritis	1 month Rx methotrexate
STX239201 United States/ Consumer	bladder cancer	17	-	drug use for unknown indication	minimal information

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- = not available, AML = acute myeloid leukemia. DE = Germany, MCN = manufacturer control number

[a] Not included in the briefing document prepared for the Dermatologic and Ophthalmologic Drugs Advisory Committee meeting (18 June 2008) or response to FDA request submitted to dermatology division (07 May 2008) because cases were later identified from FDA SRS/AERS database search.

[b] Not included in the briefing document prepared for the Dermatologic and Ophthalmologic Drugs Advisory Committee meeting (18 June 2008) or response to FDA request submitted to dermatology division (07 May 2008).

[c] Age reported as "child" was assumed to mean that initiation of etanercept and onset of malignancy occurred at < 18 years of age.

Table 2. Young Adult Cases: Patients Who Began Etanercept Treatment at ≤ 18 Years of Age[a] With Reported Malignancy at 18 to 22 Years of Age

MCN/Country/Source	Adverse Event by Preferred Term	Age at Event (years)	Time From Etanercept Initiation to Onset	Indications	Comments/ Confounders
Hematological					
US079325 Great Britain/ Healthcare professional	B-cell lymphoma	18	3 years	juvenile arthritis	-
US201133 United States/ Healthcare professional	acute myeloid leukaemia, lymphoma	19	1.5 years	ankylosing spondylitis	smoker, family history of breast cancer, colon cancer
Solid tumors					
US191107[a] Great Britain/ Registry	malignant melanoma	19	11 months	psoriatic arthropathy	Methotrexate etanercept was initiated at age 18 years 3 months
US241654 Great Britain/ Healthcare professional	malignant melanoma	19	14 months	psoriatic arthropathy, juvenile arthritis	-
STX198048 United States/ Healthcare professional	papillary thyroid cancer	18	4 years	juvenile arthritis	confirmed by biopsy
US071613 Germany/ Registry	thyroid cancer	18	10 months	spondyloarthropathy	diagnosis confirmed methotrexate co-suspect

- = not available, MCN = manufacturer control number

[a] One patient who initiated etanercept at age 18 years and 3 months is included.

Table 3. Patients Who Began Etanercept at < 18 Years of Age and Reported Event at ≤ 22 Years of Age Where Malignancy Could Not be Excluded

MCN/Country/Source	Adverse Event by Preferred Term	Age at Event (years)	Time From Etanercept Initiation to Onset	Indications	Comments/ Confounders
US187022 Great Britain/Registry	thyroid neoplasm	18	6 months	not specified	malignancy not confirmed methotrexate

MCN = manufacturer control number

Table 4. Patients Who Began Etanercept at < 18 Years of Age and Reported Event at ≤ 22 Years of Age Where Malignancy was Excluded or Pre-existing

MCN/Country/Source	Adverse Event by Preferred Term	Age at Event (years)	Time From Etanercept Initiation to Onset	Indications	Comments/ Confounders
US255645/ Germany/Registry	myelodysplastic syndrome	17	4 years	juvenile arthritis	considered pancytopenia after medical review due to myelosuppressive therapy
US155276 United States/ Literature	progression renal cancer	14	4 weeks	idiopathic pneumonia syndrome	history of renal cell carcinoma preceded etanercept therapy and disease progression continued through etanercept treatment

MCN = manufacturer control number

4. ENBREL® United States Prescribing Information for Malignancies, Tuberculosis, and Infections

The current approved Enbrel United States Prescribing Information (USPI) includes language related to infections, tuberculosis, and malignancies. In addition, Amgen proposed updated language within the pediatric psoriasis efficacy supplement. Excerpts from the current and proposed USPI label text regarding infections, tuberculosis, and malignancies are summarized below.

4.1 Current United States Prescribing Information

The current approved Enbrel USPI includes the following boxed warning for infections including tuberculosis:

WARNING
RISK OF INFECTIONS
*"Infections, including serious infections leading to hospitalization or death, have been observed in patients treated with ENBREL® (see **WARNINGS** and **ADVERSE REACTIONS**). Infections have included bacterial sepsis and tuberculosis. Patients should be educated about the symptoms of infection and closely monitored for signs and symptoms of infection during and after treatment with ENBREL®. Patients who develop an infection should be evaluated for appropriate antimicrobial treatment and, in patients who develop a serious infection, ENBREL® should be discontinued."*

"Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation) has been observed in patients receiving TNF-blocking agents, including ENBREL®. Tuberculosis may be due to reactivation of latent tuberculosis infection or to new infection. Data from clinical trials and preclinical studies suggest that the risk of reactivation of latent tuberculosis infection is lower with ENBREL® than with TNF-blocking monoclonal antibodies. Nonetheless, postmarketing cases of tuberculosis reactivation have been reported for TNF blockers, including ENBREL®. Patients should be evaluated for tuberculosis risk factors and be tested for latent tuberculosis infection prior to initiating ENBREL® and during treatment. Treatment of latent tuberculosis infection should be initiated prior to therapy with ENBREL®. Treatment of latent tuberculosis in patients with a reactive tuberculin test reduces the risk of tuberculosis reactivation in patients receiving TNF blockers. Some patients who tested negative for latent tuberculosis prior to receiving ENBREL® have developed active tuberculosis. Physicians should monitor patients receiving ENBREL® for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis infection."

In addition, the current approved Enbrel USPI includes the following text in the Warnings section:

WARNINGS

"In post-marketing reports, serious infections and sepsis, include fatalities, have been reported with the use of ENBREL®. Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their underlying disease, could predispose them to infections. Patients who develop a new infection while undergoing treatment with ENBREL® should be monitored closely. Administration of ENBREL® should be discontinued if a patient develops a serious infection or sepsis. Treatment with ENBREL® should not be initiated in patients with active infections, including chronic or localized infections. Physicians should exercise caution when considering the use of ENBREL® in patients with a history of recurring infections or with underlying conditions which may predispose patients to infections, such as advanced or poorly controlled diabetes (see ***PRECAUTIONS*** *and* ***ADVERSE REACTIONS: Infections****). Cases of tuberculosis have been observed in patients receiving TNF-blocking agents, including ENBREL®. Tuberculosis may be caused by reactivation of latent tuberculosis infection or new infection. Data from clinical trials and preclinical studies suggest that the risk of reactivation of latent tuberculosis infection is lower with ENBREL® than with TNF-blocking monoclonal antibodies. Nonetheless, postmarketing cases of tuberculosis reactivation have been reported for TNF blockers, including ENBREL®. Patients should be evaluated for tuberculosis risk factors and be tested for latent tuberculosis infection. Treatment of latent tuberculosis infections should be initiated prior to therapy with ENBREL®. Patients receiving ENBREL® should be monitored closely for signs and symptoms of active tuberculosis. The possibility of tuberculosis should be considered, especially in patients who have traveled to countries with a high prevalence of tuberculosis or had close contact with a person with active tuberculosis. All patients treated with ENBREL® should have a thorough history taken prior to initiating therapy."*

The ADVERSE REACTIONS section of the current approved Enbrel USPI describes infections reported in clinical trials and includes the following statement describing tuberculosis reported in clinical trials:

ADVERSE REACTIONS

"In global clinical studies of 20,070 patients (28,308 patient-years of therapy), tuberculosis was observed in approximately 0.01% of patients. In 15,438 patients (23,524 patient-years of therapy) from clinical studies in the US and Canada, tuberculosis was observed in approximately 0.007% of patients. These studies include reports of pulmonary and extra-pulmonary tuberculosis (see ***WARNINGS****)."*

In the current approved Enbrel USPI, language regarding malignancies is divided between the WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections. Text within the WARNINGS and ADVERSE REACTIONS sections summarize lymphoma and malignancy data from 30 studies across the rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and psoriasis indications (data cut-off of 31 December 2003). The current Enbrel USPI also warns against the use of etanercept in patients with Wegener's granulomatosis receiving immunosuppressive agents and in patients receiving concurrent cyclophosphamide.

In addition, the following text is included under Immunosuppression in the PRECAUTIONS section:

PRECAUTIONS
Immunosuppression
"Anti-TNF therapies, including ENBREL®, affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses."

*"The impact of treatment with ENBREL® on the development and course of malignancies, as well as active and/or chronic infections, is not fully understood (see **WARNINGS: Malignancies**, **ADVERSE REACTIONS: Infections**, and **Malignancies**)"*

4.2 Proposed Changes to the United States Prescribing Information in the Pediatric Psoriasis Efficacy Supplement

In early 2008, label text regarding malignancies was drafted based on a broader experience of 45 clinical studies across all indications and proposed as updated text under WARNINGS AND PRECAUTIONS as part of the pediatric psoriasis supplement.

WARNINGS AND PRECAUTIONS

Malignancies

"The role of TNF-blocking therapy in the development of malignancies is not known. In the controlled portions of clinical trials of TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared to control patients. The risk for the development of lymphomas or other malignancies in patients treated with a TNF blocker cannot be excluded."

The proposed label text includes a summary of lymphomas and other malignancies based on up to 10 years of clinical trial experience in adult patients across 45 Enbrel clinical studies (this proposed text not provided here).

The proposed label text also includes a summary of up to 8 years of clinical trial experience in pediatric patients as follows:

"In clinical trials of 696 patients for up to 8 years, representing 1282 patient-years of therapy, no malignancies, including lymphoma, have been reported."

In addition, the following text is proposed under WARNINGS AND PRECAUTIONS under Immunosuppression:

Immunosuppression

"TNF mediates inflammation and modulates cellular immune responses. TNF-blocking agents, including Enbrel, affect host defenses against infections. The effect of TNF inhibition on the development and course of malignancies is not fully understood."

5. REFERENCES

To facilitate the exchange of information and to provide support for data provided in the briefing document of 14 May 2008, the following is a bibliography for all references cited in the briefing document (the majority of which are duplicated from Section 9 of the original briefing document), along with a bibliography for the Sponsor presentation scheduled for 18 June 2008.

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