

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)

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EXECUTIVE SUMMARY

The ~~Division of Gastroenterology Products (DGP, HFD-180)~~ consulted the Division of Drug Risk Evaluation (DDRE) to review and comment on six deaths in Abbott continuation clinical trials on Humira in psoriasis (Ps) patients. They also requested a comparison of these deaths in Ps patients to the US Ps population and the US population in general using Standardized Mortality Ratios (SMR).

Ps affects 1-5% of the worldwide population and psoriatic arthritis (PsA) may be associated with Ps in up to 42% of patients^{1,2}. Humira® (adalimumab) is indicated in adults for moderately to severely active rheumatoid arthritis, for psoriatic arthritis, ankylosing spondylitis, and Crohn's Disease. It is self-administered subcutaneously, usually 40 mg every week to every other week. Humira® has a pregnancy category B but no adequate and well-controlled studies have been done in pregnant women³.

The All Adalimumab Treatment group from Abbott's open label continuation studies of the clinical trials in the treatment of moderate to severe plaque Ps had 1,696 subjects exposed to adalimumab with a total of six deaths⁴. The time frame for the study was not stated but the deaths occurred between August 2003 and December 2006. There were no deaths among the placebo controlled trials of 1,469 patients with 966 exposed to adalimumab and 503 controls. Of the six adalimumab deaths, five were males and one was female. The age range was 44 to 82 years. Only the female was from the US and of the five men, four were from Canada and one from Spain⁵. The time from first Humira exposure to adverse event or death ranged from months (five of the six cases) to more than a year (fatal metastatic gastric adenocarcinoma), and the time from last Humira dose to death ranged from 5 days to 5 months. The causes of death were: cerebrovascular accident, suicide, metastatic stomach adenocarcinoma, myocardial infarction, metastatic melanoma, and cholecystectomy. The warning section of Humira's label lists fatalities with tuberculosis, ☐ ☐

The data on these six deaths do not provide overwhelming evidence that they are directly related to Humira⁶. The diversity of causes of death and the length of time in months from first dose to the fatal adverse event make it difficult to attribute the cause of death to adalimumab.)

The Standardized Mortality Ratio (SMR) is the observed number of deaths divided by the expected number of deaths using rates from a similar population. Although calculating SMRs is inappropriate in this circumstance due to unrepresentativeness of the clinical trial data and the single US death (small number), SMRs were used to compare the adalimumab-exposed Ps deaths to the comparison populations⁷⁻¹³. Although all but two of the SMRs were less than one, suggesting a possible lower risk of death in the adalimumab-exposed Ps patients than expected in the comparison populations, comparing these six deaths from continuations of clinical trials to US populations is not reliable. Clinical trial populations, because of their inclusion criteria, are not representative of the US population or, in this case, the US Ps population. In addition, the statistical SMR calculation is designed to compare the mortality of similar groups, usually in the same geographic area and usually by 5- to 10-year age groups; thus calculating SMRs using very different populations is very unreliable in this circumstance.

The limitations of this exercise (foreign data included in the adalimumab-exposed Ps group and six deaths, other differences with comparison groups, broad age groups of study subjects, small numbers of adalimumab-exposed deaths) essentially render the error-prone SMR findings of limited utility.

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1 BACKGROUND/HISTORY

Psoriasis (Ps), affecting 1-5% of the worldwide population, is a chronic, recurring disease of thick, scaly patches or plaques in the epidermis and is thought to be an immunologic disease. Plaque Ps is the most common type of Ps (75-80%). Psoriatic arthritis (PsA) may be associated with Ps in up to 42% of patients^{1,2}.

Treatment of Ps, depending on the extent and severity of the disease, includes^{1,2}

- Topical drugs: skin moisturizers/emollients, corticosteroids, vitamin D derivatives (calcipotriene), keratolytic agents (anthralin/tazarotene, coal tar and retinoids) and patch-thinning agents (such as salicylic acid)
- Phototherapy: psoralens plus ultraviolet A (PUVA) or ultraviolet B (UVB) treatments)
- Systemic therapy: cyclosporine, methotrexate and acitretin or synthetic retinoids which has toxic effects on other body systems.

These therapies are rotated depending on the toxicities and the disease status.

Adalimumab (Humira[®]) is a recombinant monoclonal antibody, a human immunoglobulin (IgG1), one of the tumor necrosis factor-alpha (TNF- α) inhibitors. TNF- α and activated T lymphocytes are found in psoriatic plaques. Another TNF- α inhibitor, infliximab, is already labeled for plaque Ps.

Humira[®] (adalimumab) is indicated in adults for moderately to severely active rheumatoid arthritis, for psoriatic arthritis, ankylosing spondylitis, and Crohn's Disease. It is self-administered subcutaneously, 40 mg every week to every other week except in Crohn's Disease where it is given 160 mg, then 80 mg once followed by 40 mg for maintenance every other week³.

Summary of adverse events in the Humira[®] labeling³:

- Warnings and Precautions section: Serious infections, sepsis, tuberculosis, opportunistic infections, fatalities, malignancies, lymphomas, non-melanoma skin cancer, hypersensitivity reactions including anaphylaxis and angioneurotic edema, Hepatitis B virus reactivation, demyelinating disease, pancytopenia, thrombocytopenia, leucopenia, serious infections with anakinra, congestive heart failure, lupus-like syndrome, lower anti-influenza antibodies in patients receiving Humira, immunosuppression
- Adverse reactions section had many other conditions listed
- Drug interactions with anakinra, live vaccines, and methotrexate

Humira[®] has a pregnancy category B but no adequate and well-controlled studies have been done in pregnant women³.

Abbott Laboratories sponsored several clinical trials in the US, Canada, and Europe on the adalimumab treatment of moderate to severe plaque Ps. The safety information was from 1,469 patients in three placebo-controlled trials (966 on adalimumab, 503 on placebo) and two continuation studies (All Adalimumab Treatment group) with 1,696 patients, all on adalimumab for an average duration of one year, maximum duration of three years. There were no deaths observed in either arm of the placebo-controlled group. The All Adalimumab Treatment group had six deaths among the 1,696 subjects, three of which were considered 'treatment emergent' (within 70 days of the last adalimumab dose). The causes of death in the All Adalimumab Treatment group were (first three listed are 'treatment emergent'): cerebrovascular accident, suicide, metastatic stomach adenocarcinoma, myocardial infarction, metastatic melanoma, and cholecystectomy⁴⁻⁶.

This review contains comments on the six deaths in the All Adalimumab Treatment group (Ps patients on Humira) and a discussion on the calculated standardized mortality ratios (SMRs) using mortality data from the general US population and published Ps data to assess whether these six deaths are greater than expected.

2 METHODS: EVALUATION OF DEATHS & SMRS

2.1 ALL ADALIMUMAB TREATMENT GROUP

The six deaths to be evaluated in this review came from the All Adalimumab group of 1,696 patients who met the inclusion criteria for the Abbott continuation trials on moderate to severe plaque Ps patients treated with adalimumab^{4,5}. These patients were selected to assess drug efficacy and are not representative of the US population. The information on these deaths came from Abbott data submitted to the FDA⁴⁻⁶. The MedWATCH forms, the available MedWATCH follow-ups, the handwritten study case report forms, and the typed "Subject narrative" summaries were reviewed for each of the six deaths. All death reports were very brief and the information for the same case was sometimes incomplete or contradicted the information in the other reporting formats. The latest follow-up report was considered the most accurate for purposes of this review.

A brief summary of each death is listed in the Appendix. Each report of death was evaluated for an association with adalimumab for the cause of death. Information on the age, gender, country of origin, adalimumab exposure, comorbidities, concomitant medications and reported causes of death are tabulated and commented on in the Results section of this review.

2.2 STANDARDIZED MORTALITY RATIOS

Overall age-unadjusted Standardized Mortality Ratios (SMRs), were calculated to assess whether the observed deaths in the All Adalimumab Treatment group (although only 1 US death) were unexpected as compared with the general US population and with published Ps populations⁷⁻¹¹. The information for the US general population was obtained from data available online from the US Census and the Centers for Disease Control⁸⁻¹¹. The Ps population information was abstracted from literature articles on studies in US hospitalized Ps patients¹¹, US Ps patients^{11,12}, and Canadian Ps patients¹³. The comparison populations were chosen from available time periods that were similar to the time periods of the Abbott trials. With limited information available, there was no way to assure the comparability of the observed population (All Adalimumab group) to the general population from which expected rates were obtained. As a result, extreme caution is advised in interpreting the results of the SMR analysis.

A SMR is the observed number of deaths divided by the expected number of deaths as calculated using the death rates observed in a larger, similar population⁷. The comparison population death rates are applied to the All Adalimumab Treatment group population (or sub-population) to obtain the expected number of deaths. Different comparison populations were used to calculate the SMRs for each sub-group of adalimumab deaths (overall, by gender, and by age group) to obtain a range of comparison populations that were most similar to the adalimumab-exposed patients. Due to limited information for age in the overall study population, calculated SMRs were not age-adjusted.

SMRs less than one suggest a lower death rate in the adalimumab-exposed patients than expected in the comparator population. However, there are several limitations to interpreting SMRs in this review. The effects of random variation due to low numbers of deaths may influence the SMRs and therefore caution should be used when interpreting SMRs. Also, SMRs should be calculated using a representative comparison group similar to the adalimumab death group such as geographic area, age groups, and other characteristics⁷.

3 RESULTS AND DISCUSSION OF REVIEW

3.1 ALL ADALIMUMAB TREATMENT GROUP

Of the 1,696 patients, all exposed to adalimumab, in the All Adalimumab Treatment group⁵, two thirds were male, 56.3% were 44-64 years old and 6.0% were over 65 years. There were six deaths, five were males and one was female. Their ages ranged from 44 to 82 years. Only one death, the female, was from the US, the rest of the deaths were foreign, all males, one from Spain and four from Canada. The deaths occurred between August 2003 and December 2006. Doses of adalimumab were usually 40 mg given weekly or bi-weekly. The time from first adalimumab exposure to adverse event or death ranged from months (5 of the 6 cases) to more than a year (fatal metastatic gastric adenocarcinoma). The time from last Humira dose to death ranged from 5 days to 5 months. The causes of death were different for each case: cerebrovascular accident, suicide, metastatic gastric adenocarcinoma, myocardial infarction, metastatic melanoma, and cholecystectomy. Note that only one death was from the US: a white obese female, aged 62, who had been on isoniazid for eight months, had her Prozac changed to Cymbalta and was diagnosed with "sensory axonal peripheral neuropathy" the month before she died following complications from a cholecystectomy for gall stones (reports were very brief).

Although the labeling includes fatalities, malignancies and congestive heart failure as the possible adverse events, it is not clear what role that adalimumab had in contributing to these deaths. The underlying medical conditions and concomitant medications were important risk factors. The small number of deaths and variety of causes of death make it difficult to attribute adalimumab as a major risk factor in these deaths.

The six deaths in the adalimumab groups of the clinical trials in Ps patients are summarized in Table 1 below (also see short descriptions of the six death cases in the Appendix) although Abbott's individual death reports are very brief with many corrections and inconsistencies in the documents.

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Table 1. Deaths in Psoriasis Patients on Adalimumab from Clinical Trials

Age, Gender, Country	Humira Dosing & Duration	Time from Humira first and last dose	Medical Condition(s), Medications, other factors	Fatal Event(s) & Other Information
46 yo M Canada	Humira weekly May 13, 2003 to Dec 2, 2003	6.5 months from first dose 1-5 days since last dose	Hypertension Obesity Cigarette smoker Cardiomegaly Arteriosclerosis	Cerebrovascular accident - died - probably thrombus from L carotid with arteriosclerosis
50 yo M Canada	Humira every 2 weeks Mar 11, 2005 to mar 3, 2006	1 year & 2 months from first dose 2 months since last dose	Depression Anti-depressants Venlafaxine Hypertension	Suicide - died - probably from depression or anti- depressive meds
44 yo White M Canada	Humira, 40 mg weekly from Mar 17, 2003 to Aug 16, 2003	5 months from first dose to gastroscopy; 1 yr & 9 mo to death; 4 months since last dose	Peptic ulcer Smoking of cigarettes, pipe and cigars for 32 years	Fatal metastatic stomach adenocarcinoma - died following gastroscopy and stomach biopsy,
70 yo M Canada	Humira, 40 mg every 2 weeks from Apr 13, 2005 to Dec 6, 2006	1 year & 7 months since first dose 5 days since last dose	Hypertension Cardiomegaly with LVH Hypercholesterolemia Obesity Probable Atherosclerosis	Myocardial infarction - died possible factors: hypertension, cardiomegaly & L Vent hypertrophy, hypercholesterolemia, obesity
82 yo White M Spain	Humira, 40 mg weekly from Mar 21, 2006 to May 17, 2006	6 months from first dose 4 months since last dose 290 days from first dose, 170 days from last dose	Hypertension Renal insufficiency Cardiac & respiratory insufficiency with pericardial effusion Suspected TB being treated	Metastatic Melanoma - died on Etiology of death possibly related to hypertension, renal insufficiency & atheromatous plaques
62 yo White F USA	Humira, 40 mg every 2 weeks from May 16, 2005 to Dec 12, 2005	290 days (10 months) from first dose 169 days from last dose	Possible surgical complications Obesity	Cholecystectomy, Gall stones - died - Cholecystectomy, Gall stones - died -

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3.2 STANDARDIZED MORTALITY RATIOS

Death rates for the six deaths out of the 1,696 adalimumab exposed Ps patients were calculated for the overall group and for the various sub-groups (male, female, 44-64 year olds, 65 years old and over) in the clinical trials. They are reported as the number of deaths per 100,000 subjects in their particular population (See Table 2).

The SMR is used to compare mortality between different causes of death in the same geographic area. The limitations of the SMR are that small numbers make interpretation difficult and that it should not be used to compare populations from different geographical areas⁷. Patients in clinical trials are usually highly selected to assess drug efficacy and usually do not meet the comparability criteria for applying SMRs to that population. Because death rates based on small numbers are unstable, more stable death rates from larger comparison populations, the US general population and the published Ps populations, were used to calculate the expected number of deaths in the All Adalimumab Treatment group. Table 2 lists the number of deaths, number in the population, death rates, number of expected deaths in the All Adalimumab Treatment group, and the calculated SMR for the different All Adalimumab Treatment group sub-populations and their various comparative populations.

With two exceptions, all of the SMRs (0.16 – 0.59) are less than one for the adalimumab-treated Ps patients when compared to other populations (total US 2004 population, US 2004 males, US 2004 females, US 2004 40-64 year olds, US 2004 over 65 year olds, published Ps populations in US multi-center and Canadian studies). This suggests that the Ps patients have a lower risk of death than expected in the comparison populations. The two exceptions (SMRs = 3.33 and 552.77) were observed when the SMR was calculated for the US Ps population from a sample of US hospitals and from the US nationwide Ps deaths and Ps death certificates¹¹. As discussed by Pearce et al¹¹ the hospitalized Ps patients came from a sample of US hospitals and probably had more severe Ps than found in the general US, mostly ambulatory, Ps population (SMR was 3.33). The general US population data (SMR 552.77) was from the National Center for Health Statistics (NCHS) worktables compiled from death certificates. Even though they believed these data represent over 90% of the US deaths nationwide, death certificates contain subjective information from different physicians and did not include secondary diagnoses which may have been a factor in the deaths and they do not include other factors contributing deaths. In these two instances of SMRs over 1.0, the six observed adalimumab deaths (but only 1 was US) were greater than the expected number of deaths based on the comparison populations.

The main limitations of calculating SMRs based on US mortality data is that there was only one US adalimumab Ps death and the rest of the deaths were foreign whereas the comparison populations were from the general US population. A small number of cases leads to uncertainty in the generalizability of the results. Another limitation is that patients participating in the clinical trials may not be a representative sample of the US population or even of the US Ps population from which expected rates are obtained. In addition the time frames were different for the adalimumab group (more than a year), the US general population (one year, 2004), and the Ps populations (multiple years depending on the published study). The age groups varied: adalimumab group was 44 years old or older, the general US population was 20 years old or older and the Ps populations were 15 years old or older. One of the comparison groups was foreign¹³ and another comparison group was only hospitalized US Ps patients¹¹. One should be very cautious in interpreting data with such small numbers, especially when the available All

Adalimumab Treatment age groups were fairly broad (44-64 years old and over 65 years old) and when comparing a very selective international group of deaths to the whole US population.

The limitations of this exercise (foreign data included in the adalimumab-exposed Ps group and six deaths, other differences with comparison groups, broad age groups of study subjects, small numbers of adalimumab-exposed deaths) essentially render the error-prone SMR findings of limited utility.

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Table 2.	Deaths:	Deaths	Population	Death Rate per 100,000 persons per year	Expected Deaths	Calculated or Reported SMR	References
Deaths: Psoriasis Patients Exposed to Adalimumab With Comparison Populations & Standardized Mortality Ratios	Adalimumab in Ps, 44 and over, 5M:1F, 2 over 65	6	1,696	353.77			
	US Population, 2004, all deaths	2397615	299402472	800.80	13.58	0.44	cdc.gov/nchs
	US Population over 20 years old	2344008	212103606	1105.12	18.74	0.32	wonder.cdc.gov
	Adalimumab in Ps, male	5	1131	442.09			
	US Population, 2004, male deaths	1181668		955.70	10.81	0.46	cdc.gov/nchs
	US Population, 2004, male deaths over 20 years old	1149350	102778737	1118.28	12.65	0.40	wonder.cdc.gov
	Adalimumab in PS, female	1	565	176.99			
	US Population, 2004, female deaths	1215947		679.20	3.84	0.26	cdc.gov/nchs
	US Population, 2004, female deaths over 20 years old	1194658	109324869	1092.76	6.17	0.16	wonder.cdc.gov
	Adalimumab in Ps, 44-64 years	4	955	418.85			
Literature	US Deaths, Age 45-64, 1996	442394	70697728	708.00	6.76	0.59	diastercenter.com/cdc
	US Deaths, Age 45-64, 2004			625.75	5.98	0.67	wonder.cdc.gov
	Adalimumab in Ps, over 65 years	2	102	1960.78			
	US Deaths, Age over 65, 1996	1755669		5071.40	5.17	0.39	diastercenter.com/cdc
	US Deaths, Age over 65, 2004		36,293,986	4837.36	4.93	0.41	wonder.cdc.gov
	Adalimumab in Ps, 44 and over, 5M:1F, 2 over 65	6	1,696	353.77			
	US hospitalized Ps, 20% sample, 1988-2001 1.5% died/14 yrs	7	471	106.16	1.80	3.33	Pearce 2006 ¹¹
	US psoriasis pts, 1999-2001, NCHS/death certs data, 3 yrs	87 over 3 years	Not reported	0.64	0.01	552.77	
	Adalimumab in Ps, 44 and over, 5M:1F, 2 over 65	6	1,696	353.77	10.17	0.59	Ali 2007 ¹³ -compared to Ontario pop
	U Toronto Ps Arth Clinic, 1978-2004, death rate 15.6% / 26 yrs	106	680	599.55		1.36 (1.12, 1.64)	
U Toronto Ps Arth, male	51				1.25		
U Toronto Ps Arth, female	55				1.47		
Adalimumab in Ps, 44 and over, 5M:1F, 2 over 65	6	1,696	353.77	22.00	0.27		
US Multi-ctr, Ps pts, 1976-1986, over 10 yrs (13224 PY)	179	1380	1297.10		0.94 (0.8, 1.1)	Stern 1998 ¹²	
US Multi-ctr, Ps pts, 1976-1986, males	127				compared to matched pop		
US Multi-ctr, Ps pts, 1976-1986, females	52						

4 SUMMARY AND RECOMMENDATIONS

Six deaths occurred in the 1,696 adalimumab exposed patients from the continuation studies of the Ps clinical trials. No deaths were noted in the placebo-controlled clinical trials. There were no unifying factors noted among the deaths reported. Of the six deaths, only the female was from the US, the rest, all males, were foreign. The causes of death were: cerebrovascular accident, suicide, metastatic stomach adenocarcinoma, myocardial infarction, metastatic melanoma, and cholecystectomy. The warning section of Humira's label lists fatalities with tuberculosis,

□ The data on these six deaths do not provide overwhelming evidence that they are directly related to Humira. The diversity of causes of death and the length of time in months from first dose to the fatal adverse event make it difficult to attribute the cause of death to adalimumab. b(4)

Although SMRs should be applied to populations from the same geographic area and should not be used for small numbers of deaths, SMRs were calculated using the clinical data which is not representative of the US. For the six adalimumab-exposed deaths (one US, five foreign) compared to the general US population, the SMRs for the various sub-groups were all less than one suggesting that the number of adalimumab deaths is less than expected for the general US populations. SMRs calculated for the six adalimumab-exposed deaths compared to published Ps populations were less than one except for the two SMRs using data on the nationwide US Ps patient population. There are several possible reasons for this discrepancy, the main one being that there was only one US death. Other possible reasons are differences in time frames for the studies, ages of patients, severity of Ps (hospitalized versus outpatients), limitations of death certificate data, and the representativeness of the groups to the US general population.

This exercise in calculating SMRs for adalimumab-exposed deaths using various comparison populations suggests that adalimumab-exposed Ps deaths are probably not more than expected in US populations or Ps populations. Clearly this exercise is fraught with limitations and the findings are not appropriate when more robust data are available. The limitations are:

- The numbers of adalimumab-exposed Ps deaths are very small
- Most of the death cases were foreign whereas the comparator populations were US based
- Patients volunteering for clinical trials are highly selected and may not be representative of the general population
- Comparison groups probably have differences in characteristics from the adalimumab-exposed Ps sub-groups that may influence the calculated SMRs (time frame of study, age groups, geographic location)
- Age-adjustment of the SMRs was limited to only two large age groups

SMRs are really not appropriate for evaluating these six adalimumab Ps deaths for the limitations listed above; therefore, caution is recommended when using the findings of this exercise. However, the trend of the SMRs across sub-groups is toward suggesting that the number of adalimumab-exposed Ps deaths is less than expected when compared to all deaths in the US general population or to selected Ps populations.

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APPENDIX

The following are descriptions of the six adalimumab-exposed deaths from the continuation studies of the Ps clinical trials:

1. 46 year old male, Canada, Humira weekly May 13, 2003 – Dec 2, 2003 (6 month exposure).
Died of cerebrovascular accident on [redacted] [redacted]
[redacted] [redacted] with onset of symptoms 4-7 days prior to death, etiology stated as probably from a left carotid artery thrombus. **b(6)**
Indication for Humira & Abbott study: psoriasis since 1975 & psoriatic arthritis since 1999 – right hand, ankle, knee; M02-528 since May 13, 2003 with blinded study drug weekly for 12 weeks, continued in M02-528 since Aug 6, 2003; Patient #2325.
Other medical conditions: Hypertension – on Lopressor (hydrochlorothiazide, metoprolol tartrate) since 1998 and “Novohydiazide” since 1998; Obesity, 144 kg; Arthroscopy 1976; pneumothorax 1984; Cigarette smoker for 23 years, stopped in 1983; Alcohol intake <2 drinks per day; Squamous cell cancer removed in 2000; Autopsy: mild cardiomegaly, arteriosclerosis of terminal descending aorta, dilation and thrombus in left carotid.
Medications other than Humira: Metoprolol tartrate (Lopressor) for hypertension, Naproxen for arthritis, Multivitamins, Glucosamine, Sulfasalazine for arthritis, Imitrex for migraine, Rizatriptan (Maxalt) for migraine, Hydrochlorothiazide for hypertension, Tylenol Sinus Med for sneezing, Benadryl Plus for upper respiratory tract infection, Polysporin Drops for eye infection, topical corticosteroids, phototherapy Dec 2002 – Dec 2003.
2. 50 year old male, Canada, Humira, probably 40 mg every 2 weeks from Mar 11, 2005 to Mar 3, 2006 (1 year exposure).
Died from suicide on [redacted] [redacted] **b(6)**
Etiology of death possibly depression and also possibly anti-depressants.
Indication for Humira & Abbott study: Psoriasis; M03-656 from Mar 11, 2005 to Mar 3, 2006 with blinded study drug every 2 weeks; Patient #4405.
Other medical conditions: Major depression (burnout) since 2004; Hypertension since 2000; Epidermal cyst on left back with drainage since 2005; Cigarette smoker, one pack per day for 25 years; no alcohol.
Medications other than Humira: Venlafaxine for depression (Effexor with black box on suicide in young adults), Gabapentin for depression (Neurontin, indicated for postherpetic neuralgia and epilepsy with warnings for behavioral problems, hostility, thought disorder in children), Oxazepam for depression, topical corticosteroids, phototherapy 1998 - 2005.
3. 44 year old male, Canada, Humira, 40 mg weekly from May 2, 2003 to Aug 16, 2003 (3 months exposure).
Died of fatal metastatic stomach adenocarcinoma on [redacted] [redacted] **b(6)**
[redacted] [redacted] following gastroscopy and stomach biopsy on [redacted] [redacted] **b(6)**
[redacted] [redacted] for weight loss, pyrosis, nausea and vomiting. Etiology probably peptic ulcer disease and smoking of cigarettes, pipe and cigars for 32 years.
Indication for Humira & Abbott study: Psoriasis; Study M02-528 for 12 weeks from May 2, 2003 to Jul 24, 2003 with blinded study drug weekly and M02-529 study drug for 3 weeks then discontinued one month before event (as reported); Patient #2007.
Other medical conditions: Peptic ulcer disease 1993; Hypertension 2002; Facial bone fracture with metal plate open reduction 1981; Appendicitis 1985; Nose fracture and rhinoplasty 1986; Kidney stones 1987; Herniated spinal disc 1996; Hypercholesterolemia 2000; Inguinal **b(6)**

hernia repair bilaterally 2001; PPD positive but CXR normal April 2003; Smoker of cigarettes (2 packs per day), pipe and cigars for 32 years; Alcohol intake light.
Medications other than Humira: Isoniazid for tuberculosis prophylaxis (PPD +), Paracetamol as needed for headache or back pain; Telmisartan for hypertension; Rofecoxib for back pain; Esomeprazole for dyspepsia; Ibuprofen for back pain; Tazarotene for psoriasis; Rabeprazole for stomach pain.

4. 70 year old male, Canada, Humira, probably 40 mg every 2 weeks from Apr 13, 2005 to Dec 6, 2006 (1 year 6 months exposure).

Died from myocardial infarction on [redacted] since last dose). Etiology of death probably due to hypertension, cardiomegaly with left ventricular hypertrophy, hypercholesterolemia, morbid obesity, and probable coronary artery occlusive disease in elderly. No autopsy. Pt was on meloxicam (boxed warning for cardiovascular thrombotic events, MI & stroke). b(6)

Indication for Humira & Abbott study: Psoriasis and psoriatic arthritis; Study M03-656 since Apr 13, 2005 to Nov 16, 2005 with blinded study drug, continued in M03-658 Dec 7, 2005 until Dec 6, 2006 (week 47); Patient #2885.

Other medical conditions: Wrist fracture 1947; Migraine headaches 1957; Psoriatic pruritus 1980; Hypothyroidism 1985; Nearsighted 1985; Cholecystitis 1981; Cholecystectomy 1989; Proteinuria 1999; Gastroesophageal reflux disease 2000; Hypoandrogenism 2000; Hypercholesterolemia 2003; Hypertension 2003; Cardiomegaly with left ventricular hypertrophy 2005; nonsmoker; nondrinker of alcohol.

Medications other than Humira: Losartan (COZAAR) for hypertension; Omeprazole for gastroesophageal reflux disease; Thiamine for foot numbness; Paracetamol (Losec) for psoriatic arthritis; Atorvastatin (Lipitor) for hypercholesterolemia; Eltroxin for hypothyroidism; Andriol gel for hypoandrogenism; Meloxicam (NSAID with boxed warning for cardiovascular thrombotic events, MI & stroke for psoriatic arthritis); Robaxacet for muscle strain; Tetracycline for peri-oral dermatitis.

5. 82 year old white male, Spain, Humira, 40 mg weekly from Mar 21, 2006 to May 17, 2006 (2 months exposure).

Died [redacted] after the last Humira dose. Etiology of death possibly related to hypertension, renal insufficiency with renal atheromatosis and atheromatous plaques having proteinuria since [redacted] cardiac & respiratory insufficiency with pericardial effusion since Jul 2006, suspected TB treated since [redacted] also mediastinic adenopathies on right axilla with right pleural discharge; biopsy of axillary lymph node showed metastasis of malignant melanoma. b(6)

Indication for Humira & Abbott study: Psoriasis, chronic plaque; Study M04-716 double blind placebo controlled on study drug from Nov 22, 2005 to Mar 10, 2006 (119 days); continued in open label study Mar 21, 2006 on drug 40 mg every other week until May 17, 2006; Patient #16404.

Other medical conditions: Hypertension 1998; Renal insufficiency May 2006; Cardiac & Respiratory insufficiency with pericardial effusion Jul 2006; suspected pulmonary TB treated since [redacted] Deafness 1998; Nonsmoker and nondrinker of alcohol; Renal insufficiency, anemia, pulmonary discharge and pericardial discharge [redacted] Weight 105 kg.

Medications other than Humira: Enalapril for hypertension; Indapamide for hypertension; Folic acid; Erythropoietin for anemia; Furosemide for renal insufficiency; TB treatment; Lorazepam for insomnia; Pantoprazole for gastric protective; Pyrazinamide for probable TB;

Prednisone for renal insufficiency; Rifampicin for probable TB; Heparin for thrombosis prevention; Paracetamol for headache.

6. 62 year old white female, USA, Humira, 40 mg every 2 weeks from May 16, 2005 to Dec 12, 2005 (7 months exposure).

Died with gall stones c

Etiology of death possibly related to complications related to abdominal surgery (cholecystectomy) for cholelithiasis, obesity.

Indication for Humira & Abbott study: Psoriasis with pruritus; Study M03-656 on blinded study drug from May 16, 2005 to Aug 30, 2005 (15 weeks reported as 120 days) then in open label continuation study M03-658 from Sep 13, 2005 to Dec 12, 2005; Patient #450.

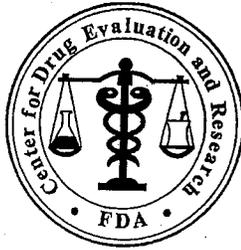
Other medical conditions: Sensory axonal peripheral neuropathy Feb 2006; Depression treated with Fluoxetine since May 1997; Arthritis of hands 1998; Hypertension 1999; Hypothyroidism 2000; Sleep apnea 2001; Insomnia 2002; Restless leg syndrome 2003; Obesity (124 kg) April 2005; Edema of lower legs; Esophageal ulcers 1987; Intra uterine device placement; Murmur 1946; Rheumatic fever 1946; Ex-smoker (1 pack per day for 20 years) quit in 1996; Alcohol light drinker (<2 drinks per day).

Medications other than Humira: Cyanocobalamin (vitamin B12) for neuropathy; Isoniazid 8 months prior for TB prophylaxis; Pyridoxine (vitamin B6) for neuropathy; Neurontin; Cymbalta; Tylenol PM for insomnia; Hyzaar for hypertension; Levothyroxine for hypothyroidism; Fluoxetine (Prozac) for depression; Progesterone and Estradiol for hormone replacement; Galiximab (possibly "baliximab") over 12 months before; corticosteroids, phototherapy.

Carolyn A. McCloskey

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Division of Drug Risk Evaluation, HFD-430

b(6)



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: November 5, 2007

To: Susan Walker, M.D., Director
Division of Dermatology and Dental Products

Thru: Toni Piazza-Hepp, Pharm.D., Associate Director
Division of Surveillance, Research and Communication Support *Jodi Durham* 11/5/07

From: Sharon R. Mills, BSN, RN, CCRP *Sharon R. Mills* 11/5/2007
Patient Product Information Specialist
Division of Surveillance, Research and Communication Support *Toni Piazza-Hepp*

Subject: DSRCS Review of Patient Labeling (Medication Guide and Patient Instructions for Use)

Drug Name(s): Humira (adalimumab) solution for subcutaneous injection

Application Type/Number: BLA #125057

Submission Number: S-110

Applicant/sponsor: Abbott Laboratories

OSE RCM #: 2007-1813

have different risk profiles. Patients should be provided with information upon which to make an informed decision as to the best treatment of their psoriasis.

The sponsor revised the currently approved Patient Information with Patient Instructions for Use, into a Medication Guide which includes Patient Instructions for Use, and reflects the changes for this supplement. The Medication Guide and Patient Instructions for Use were submitted to FDA on October 5, 2007. DSRCs has been requested to review the Medication Guide and Patient Instructions for Use.

2 MATERIAL REVIEWED

Revised proposed Package Insert dated November 1, 2007 forwarded by the Review Division, which includes the sponsor's proposed changes to the Professional labeling, Medication Guide and Patient Instructions for Use, for this supplement submitted on March 23, 2007, appended to the currently approved Package Insert, dated November 9, 2007.

3 DISCUSSION

See the attached document for our recommended revisions to the proposed Medication Guide and Patient Instructions for Use for HUMIRA (adalimumab). We have simplified the wording where possible, made it consistent with the Package Insert (PI), removed unnecessary wording, moved language to appropriate sections of the Medication Guide and insured that it complies with the Medication Guide Regulations as specified in 21 CFR 208.20.

Comments to the Review Division are ***bolded, underlined and italicized.***

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b(4)

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19 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)