

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
sBLA 125057/110

SUMMARY REVIEW



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

MEMORANDUM

DATE: 16Jan08

FROM: Susan J. Walker, M.D., F.A.A.D. *Susan Walker 1/16/08*
Director
Division of Dermatology and Dental Products/ODEIII

SUBJECT: Division Director Decisional Review

APPLICANT: Abbott Laboratories

DRUG: BLA 125057/ Supplement 110
Adalimumab (Humira®) 40mg for treatment of adult moderate to severe
plaque psoriasis

1. Summary

Abbott Laboratories has submitted a supplement to their biologics license application for Humira® (adalimumab) 40 mg, to include a new indication for the treatment of adult patients with moderate to severe chronic plaque psoriasis. We have completed our review of this application, as amended. I concur with the recommendations of the review team for approval of this application. The applicant has provided information to demonstrate the safety and efficacy of adalimumab in the labeled indication and the application will be approved with the agreed upon text labeling and medication guide.

Abbott Laboratories has agreed to a post marketing commitment to conduct a prospective, multi-center registry including 5000 adult psoriasis patients treated with Humira® in the United States. This registry will characterize and assess the incidence of serious adverse events (including serious infections, tuberculosis, opportunistic infections, malignancies, hypersensitivity reactions, autoimmune reactions and deaths) as well as other adverse events of interest in the study cohort.

2. Background

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences, with a molecular weight of approximately 148 kilodaltons. It binds with high affinity and specificity to soluble TNF- α and blocks its interaction with cell surface TNF receptors. The relationship between the pharmacodynamics activities and the mechanism(s) by which adalimumab exerts its clinical effects is unknown.

Humira® was approved for the treatment of rheumatoid arthritis (RA) December 2002, psoriatic arthritis in October 2005, ankylosing spondylitis July 2006, and Crohn's disease in February 2007. Dosage for the first 3 indications is 40 mg sub-cutaneously every other week (eow), and may be combined with other systemic arthritic medications. As a solo agent, it may be used at a dose of 40 mg every week in RA. In Crohn's disease, the initial dose is 160 mg at week 0, then 80 mg at week 2, followed by 40 mg every other week beginning at week 4.

3. CMC

The chemistry, manufacturing and controls review was conducted by Gurpreet Gill-Sangha Ph.D. and Patrick Swann Ph.D., and I concur with their review. As adalimumab is a currently licensed product, no additional CMC information is presented. Abbott provided drug substance, drug product batches, and the container closure used in the psoriasis trial. The information was found to be adequate.

There was discussion with regards to the use of individual syringes in the psoriasis clinical trial and post-approval use of the Humira® Pen (an integrated, disposable auto injection delivery system). The marketed product is 40mg in 0.8ml buffer formulation and it is approved in the vial, pre-filled syringe and pen injector. There is no change in formulation for the psoriasis vs. the marketed product. From a CMC perspective the two container closures are determined to be comparable as per previous supplement BLA approvals for Humira®.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology and toxicology review was completed by Carmen Booker Ph.D. and Paul Brown Ph.D., and I concur with their review. As no new nonclinical studies were submitted with this supplement, the Division relied upon previous review of nonclinical studies for the approval of adalimumab for rheumatoid arthritis.

As TNF binding studies (neutralization potency) showed that non-human primates are the most relevant species, toxicology testing in cynomolgus monkeys included a 39 week chronic toxicity study with IV administration at doses up to 214.8 mg/kg/week. At the end of the treatment period a subset of animals from the control and high dose groups were maintained for a 20 week treatment-free recovery period. The reviewer's¹ conclusion is that for clinical

¹ Pharmacology Review Application 125/057/0: Andrea Weir, PhD

signs and mortality the animals did not exhibit any treatment related effects, and that in females (but not males) the high dose females exhibited a decrease in body weight.

Two 4-week toxicity studies in cynomolgus monkeys were conducted with weekly intravenous infusions of adalimumab, using dosages ranging from 32 to 179.6 mg/kg. In both the 4 week and 39 week studies, effects included decreased cellularity of B cells (CD21) in splenic follicles. In the 39 week study, involution of the thymus was noted at doses of 82.9 mg/kg and greater. Although the thymus effects were reversible after 20 weeks of recovery the spleen effects were not entirely reversed. Spleen effects were noted even at the 32mg/kg dose, therefore a NOAEL was not established in the 38 week monkey study. The observed effects appear to be related to the pharmacologic effects of adalimumab. The doses used in the monkey study are significantly higher than the human doses used in the clinical trials for psoriasis, which are approximately 0.5 to 1mg/kg.

Long term studies of adalimumab have not been conducted to evaluate its carcinogenic potential or effect on fertility. No clastogenic effects were observed in the *in vivo* mouse micronucleus study, and no mutagenic effects were observed in the *Salmonella-Escherichia Coli* (Ames) assay. Adalimumab was found to have no effect on maternal or reproductive parameters in a developmental toxicology study. The NOAEL for maternal and reproductive toxicity was found to be 100mg/kg.

5. Clinical Pharmacology

The clinical pharmacology review was conducted by Tien-Mien Chen, Ph.D. and Sue-Chih Lee, PhD and I concur with their review.

The mean steady-state trough adalimumab serum levels (5.2-6.0 $\mu\text{g/mL}$) observed in the psoriasis trials were within the range of those observed in other indications at the same dosage schedule (40mg eow as monotherapy). The population PK analysis demonstrated that the median apparent clearance and volume of distribution were also consistent with other populations. One study (M03-656) demonstrated that the patients with a PASI75 response at week 16 had higher mean steady-state serum adalimumab levels than patients who did not achieve a PASI75 (6.28 $\mu\text{g/mL}$, 2/24 $\mu\text{g/mL}$).

The overall rate of anti-adalimumab antibody (AAA) formation in patients with psoriasis (8.4%) appeared to be in range with those demonstrated in RA (12%), Ankylosing spondylitis (8.6%) and psoriatic arthritis (13.5%). The development of AAA tended to be associated with reduced adalimumab exposure, and is consistent with other indications where a trend for higher apparent clearance in patients with positive AAA has been shown. Loss of adequate response was significantly higher in AAA+ patients than in AAA- patients.

6. Clinical/Statistical

The clinical review was conducted by Denise Cook M.D., clinical team leader was Markham Luke M.D., Ph.D., biostatistical reviewer Clara Kim Ph.D., biostatistical team leader was

Mohamed Alosh Ph.D. I concur with the clinical and biostatistical reviews. The medical officer's executive summary of safety and efficacy follows:

6.1. Efficacy

"The efficacy of adalimumab in the treatment of moderate to severe plaque psoriasis is supported by trials randomized, double blind, placebo controlled multicenter trials. Study M03-656 included multiple centers in the United States and Canada and study M04-716 included multiple centers in Europe and Canada. The trials consisted of 3 distinct periods – A, B, and C. Period A consisted of 16 weeks of treatment, followed immediately by period B in which (Short description of periods A, B, C)

Period A of trial M03-656 and trial M04-716 addresses short-term efficacy of adalimumab in the treatment of moderate to severe chronic plaque psoriasis. Twelve hundred and twelve (1212) patients with a baseline PASI ≥ 2 and BSA involvement $\geq 10\%$, were randomized 2:1 to receive adalimumab:placebo for 16 weeks. Efficacy variables used to determine efficacy were proportion of patients with a \geq PASI 75 response rate and patients with a Physician's Global Assessment (PGA) severity score of clear or minimal at 16 weeks. Trial M04-716 also randomized subjects 2:1 to receive adalimumab: placebo. Subjects with a baseline PASI ≥ 2 and BSA involvement $\geq 10\%$ were evaluated. Thus, 99 patients were treated with adalimumab and 48 with placebo. There was an additional arm of 110 patients treated with methotrexate that will not be discussed in this summary.

In trial M03-656, for the efficacy variable \geq PASI 75 response rate, 578/814 (71.0%) on adalimumab vs. 26/398 (6.5%) achieved this response rate ($p < 0.0001$). For a PGA of clear or minimum, 506/814 (62.2%) patients on adalimumab vs. 17/398 (4.3%) were a success ($p < 0.0001$). In trial M04-716, for \geq PASI 75 response rate, 77/99 (77.8%) vs. 9/48 (18.8%) achieved this response ($p < 0.0001$). For a PGA of clear or minimum the success was 70/99 (70.7%) vs. 5/48 (10.4%) with a $p < 0.0001$.

Periods B and C in trial M03-656 look at the long-term efficacy of adalimumab up to 52 weeks. Patients who attained a \geq PASI 75 response from period A were entered into Period B at week 16 and continued to receive 40 mg eow of adalimumab up to week 33. Period C is a double-blind placebo-controlled treatment period in which subjects who maintained a \geq PASI 75 response at week 33 and were originally randomized to active therapy in Period A were re-randomized (1:1) to receive adalimumab or placebo.

The Division investigated in Period C the proportion of subjects losing an adequate response after week 33 and on or before week 52. Loss of adequate response was defined as the following: subjects who did not maintain a \geq PASI 75 response, subjects who did not maintain a PGA score of "clear" or "minimal" and subjects who did not maintain either a \geq PASI 75 response or a PGA score of "clear" or "minimum". Results showed that 52/250 (20.8%) had a loss of adequate response on adalimumab compared to 138/240 (57.5%) on placebo at week 52 ($p < 0.0001$) for PASI 75. For PGA, loss of adequate response occurred in 80/250 (32.0%) as compared to 173 /240 (72.1%) on placebo at week 52 ($p < 0.0001$). The analysis demonstrates that adalimumab does maintain its efficacy in the long-term (over 52 weeks). This does not drop off over time, as in this analysis at 52 weeks, 68.0% of subjects were able to maintain a success with a PGA of clear or almost clear, which falls between the success in Period A of this trial of 62.2% and trial M04-716 where the success for PGA was 72.2% after 16 weeks of treatment. PASI 75 success was somewhat higher in all analyses. These results were all highly

statistically significant. Thus, it has been demonstrated that adalimumab can maintain its efficacy over a period of 52 weeks.”

6.2. Safety

“The evaluation of the safety of adalimumab in patients with moderate to severe chronic plaque psoriasis was obtained from 3 placebo controlled trials and 3 continuation studies. The placebo controlled study set consists of 1469 patients, 966 treated with adalimumab and 503 on placebo. Except for 45 patients in the phase 2 dose ranging study who were treated for 12 weeks, all patients in the adalimumab arms were treated with an initial dose of 80 mg sq followed by 40 mg eow sq for 16 weeks. The second study set is the all adalimumab study set which consists of 1696 subjects.

For the all adalimumab treatment set (1696 subjects), the median and mean durations of treatment were 553.0 days and 542.9 days, respectively, representing an average treatment duration of approximately 1½ years. Treatment duration was more than three years in 6.6% of subjects. Two-thirds of the subjects [1146 subjects (67.6%)] had greater than 60 weeks (15 mo) of exposure. More than half of the subjects [980 (57.8%)] had greater than 72 weeks (18 mo) of exposure and a little more than a quarter of subjects [453 (26.7%)] had greater than 96 weeks (24 mo) of exposure.

The majority of subjects were between the ages of 40-64 years (56.3%) with the median age of 44 years. The next highest group was < 40 years old (37.7%). Two-thirds of the subjects were male with the majority of subjects being Caucasian (91.8%).

In the placebo controlled study set, 86/1469 (5.8%) of subjects discontinued, 50/503 (9.9%) in the placebo arms and 36/966 (3.7%) in the adalimumab arms. The major reason for discontinuation in the placebo arms was “unsatisfactory therapeutic response”, 5%, followed by “withdrawal of consent”, 3.6%. The major reason for discontinuation in the adalimumab arms was “adverse event”, 1.8% followed by “withdrawal of consent”, 1.0%. In the all adalimumab study set, 30.0% (509/1696) of subjects discontinued from the trials. The four leading causes were “unsatisfactory therapeutic effect”, 10.8%, “withdrawal of consent”, 8.8%, “adverse event”, 6.4%, and “lost to follow-up”, 4.4%.

The overall incidence of AEs reported in the adalimumab arms (63.6%) was slightly higher than in the placebo arms (59.0%) in the pivotal trials. This difference was not statistically significant. The incidences of AEs at least possibly related to study drug (adalimumab, 22.9%; and placebo 16.9%) and infections (adalimumab, 30.3%; and placebo 23.9%) were statistically significantly higher in adalimumab-treated subjects than in placebo treated subjects. The incidence of serious infections, however, was comparable between the two, 0.5% for adalimumab and 0.8% for placebo.

The most common AEs in descending order of frequency were nasopharyngitis 7.8% in both adalimumab (ADA) and placebo (PBO), upper respiratory tract infection (6.4%ADA; 3.0% PBO), headache (6.1%ADA; 5.6%PBO), arthralgia and injection site reaction (both 2.9%ADA; 1.4%PBO). It should be noted that when one looks at corresponding exposure-adjusted rates (E/100PY), headache occurs more frequently in the placebo group. The incidence of URI was statistically more significant in the adalimumab group than in the placebo group. Arthralgia is a new adverse event for which HUMIRA® is not labeled.

The incidence of severe AEs was low in both arms, 27/966 (2.8%) in the adalimumab group and 15/503 (3.0%) in the placebo group as was the incidence of serious AEs, 18/966 (1.9%) in the ADA group and 8/503 (1.6%) in the placebo group. No subjects died in the placebo-controlled study set. Of the 15 AE categories of special interest, no subjects experienced AEs in any of the following categories: lymphoma, demyelinating disorder, opportunistic infection (excluding TB), TB, and lupus-like syndrome. There were 8 (0.8%) malignancies in the ADA group and 2 (0.4%) in the placebo group. The majority of the malignancies were due to non-melanoma skin cancer, the majority of which were BCCs, 5 in the ADA group and 1 in the placebo group. Although slightly higher in the ADA group (0.5% to 0.2%), this was not of statistical significance. The three other cancers that occurred in the adalimumab group were squamous cell carcinoma, malignant melanoma in situ, and breast cancer in patients aged 54, 40, and 71 years, respectively. The other cancer in the placebo group was bladder cancer in a 77 year old.

In the placebo controlled studies, the proportion of patients whose chemistries changed to high was slightly higher in the adalimumab group including ALT (7.8 vs. 6.3), AST (4.9 vs. 3.9), bilirubin (2.1 vs. 1.2), cholesterol (21.1 vs. 19.0), CK (8.2 vs. 5.7), and triglycerides (17.7 vs. 14.4). As far as lipid profiles, however, 0.9% of subjects treated with adalimumab reported hypercholesterolemia vs. none in the placebo group. In terms of treatment-emergent AEs per 100 patient-years of exposure, hepatic events are slightly higher in the adalimumab group, 10.2 vs. 9.5 events per 100 patient-years of exposure. Hematologic events were slightly higher in the placebo group, 0.1% vs. 0.2%.

In the All Adalimumab Treatment Set, 85.9% of subjects reported at least one treatment-emergent AE and 35% of subjects reported AEs that were considered by the Investigator to be at least possibly related to adalimumab treatment. Severe AEs were reported in 9.9% of subjects (9.2E/100PY). Serious AEs were reported in 8.2% of subjects (7.3E/100PY). AEs leading to discontinuation occurred in 7.0% of subjects (6.2E/100 PY).

The most common AEs in the All Adalimumab Treatment Set were infections (59.0%, 1000/1696), of which 2.0% were serious infections, injection site reactions, (10.0%, 170/1696), and hepatic events (4.4%, 75/1696). Malignancies occurred in 2.1% of subjects, of which 1.1% were non-melanoma skin cancers and 1.1% were other malignancies. Again, the majority of the non-melanoma skin cancers were BCCs. There were no instances of lymphoma. Four subjects (0.2%) developed opportunistic infections excluding TB and 3 subjects (0.2%) developed TB.

As stated earlier, the All Adalimumab Treatment Set includes the later study phases and subjects had an average duration of treatment of 1½ years and more than 3 years duration of treatment. In this set, the risk of AEs does not appear to increase with chronic adalimumab treatment. The rates of AEs per 100 patient-years of exposure are generally lower in the All Adalimumab Treatment Set compared with the adalimumab arm of the Placebo-Controlled Study Set, particularly for infections (86.0 vs. 134.7/100 PY), injection site reactions (13.1 vs. 29.9 E/100PY), and hepatic events (4.5 vs. 10.2 E/100PY). The exposure-adjusted AE rates for 'any malignancy' and 'nonmelanoma skin cancer' in the All Adalimumab Treatment Set (1.6 and 0.8 E/100PY, respectively) are lower compared with the adalimumab treatment group in the Placebo-Controlled Study Set (2.4 and 1.7 E/100 PY).

There were no severe AEs in the All Adalimumab treatment set that occurred at $\geq 1\%$. The highest incidence of severe AEs was cellulitis which occurred in 6/1696 (0.4%) subjects,

followed by coronary artery disease (0.3%). The other severe adverse events occurring at 0.2% were headache, breast cancer, migraine, myocardial infarction, and psoriatic arthropathy.

Six (6) deaths occurred during the open-label portions of the adalimumab trials. None of the deaths were related to known infection. The events occurred from 2 days to 190 days after receiving last treatment of adalimumab. Two were secondary to cardiovascular events, two to cancer, one to suicide, and one post-surgical. It is difficult to unequivocally attribute these deaths solely to adalimumab, as all had confounding factors. However, given that adalimumab is an immunosuppressant and is implicated across other indications with malignancy occurrence, it may have contributed to the 2 deaths associated with malignancy in the psoriasis trials."

The Office of Surveillance and Epidemiology (OSE) was asked to review and comment on six deaths in Abbott continuation trials of Humira® in psoriasis patients, with a comparison of these deaths to the US psoriasis population and the US population in general using the Standardized Mortality Ratios (SMR). I concur with the OSE and medical officer conclusion that "data on these six deaths did 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 makes it difficult to attribute the cause of death to adalimumab." Abbott has committed to a 10 year prospective registry study of 5000 adult patients with psoriasis to characterize and assess the incidence of adverse events.

I concur with the recommended dosing and administration of Humira® for adult patients with plaque psoriasis which is an initial dose of 80mg followed by 40mg given every other week starting on week after the initial dose. The use of Humira® in moderate to severe plaque psoriasis beyond one year has not been evaluated in controlled clinical studies.

7. Pediatric use/PREA waivers/deferrals

Safety and effectiveness of the use of Humira® in pediatric populations have not been demonstrated for any of the approved indications. The sponsor has requested a waiver of studies for plaque psoriasis for patients 0-4 years of age and a deferral of studies for patients 5-7 years of age. b(4)

The determination of the most appropriate pediatric plan for adalimumab is informed by the existing safety database for adalimumab compared with the perceived benefits for pediatric patients. Long term registry studies are ongoing for adalimumab. Adalimumab carries a black box warning for risk of infections, and includes warnings for malignancies, hypersensitivity reactions, Hepatitis B virus reactivation, neurologic and hematologic reactions, heart failure, autoimmunity and immunosuppression. In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving TNF-blockers compared to control patients.

Pediatric studies evaluating the safety and effectiveness of Humira® in the treatment of juvenile rheumatoid arthritis (4-17yrs) b(4) are ongoing or under review. Benefit-risk assessment for use of Humira® to treat these conditions includes the consideration that these diseases may progress and manifest permanent, irreversible and

disabling sequelae such as joint destruction, \square b(4)
The benefit-risk assessment for use of Humira® for the treatment of pediatric psoriasis does not generally include considerations of progression such that the patient has permanent, irreversible and disabling sequelae. Use of biologic treatment therapies for pediatric patients with psoriasis must include consideration of the known risks and the anticipated benefits. The full elucidation of the risk-benefit assessment in pediatric patients will be informed by information derived from ongoing controlled trials in adults, post marketing registry studies, pediatric studies for already approved indications, and other risk assessment activities.

All applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. We are waiving the pediatric study requirement for ages 0 up to 4 years because studies are impossible or highly impractical due to the small number of patients and the disease may be difficult to accurately diagnose. We are deferring submission of pediatric studies for ages 4 to 17 years for this application because discussion and design of pediatric studies should be delayed until additional safety data have been collected and reviewed. The pediatric plan is to assess data anticipated from on-going trials as well as further analysis and assessment of data, including data pertaining to the diagnosis and treatment of psoriasis in the pediatric population, and to establish a plan that incorporates this data.

8. Post Marketing Activities

Upon approval of Humira® for the treatment of moderate to severe plaque psoriasis, there will be an increase in the number of patients exposed. Post marketing safety data collection and risk assessment based on observational data will continue to inform the risk profile of adalimumab in the treatment of adult moderate to severe plaque psoriasis.

Registry Study

Adalimumab has multiple labeled warnings and precautions, including infection and association with malignancy. Routine risk minimization measures include FDA-approved professional labeling which will be updated as appropriate to incorporate information from post marketing surveillance studies or other studies. Several long term studies are underway or under review, including studies in rheumatoid arthritis (5yrs) and Crohn's disease (5000 patient, multi-center, uncontrolled observational study in adults). With this current approval, Abbott has agreed to conduct a prospective, multi-center registry including 5000 adult psoriasis patients treated with Humira® in the United States. This registry will characterize and assess the incidence of serious adverse events (including serious infections, tuberculosis, opportunistic infections, malignancies, hypersensitivity reactions, autoimmune reactions and deaths) as well as other adverse events of interest in the study cohort. All enrolled study patients will be evaluated for a period of at least 10 years with comprehensive annual reports provided to the Agency. The registry will collect data including patient characteristics, demographics and drug exposure (including dose, duration and time to onset of adverse event). The collection of data will be via active surveillance methods and data will be validated by a

review of medical records as per the guidance for industry titled *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*. The final study protocol will be submitted by March 2008 with patient accrual initiated in September 2008.

Other

Abbot will provide the final study report for the continuation study evaluating patients who completed clinical studies with Humira®. Abbott will also evaluate the effects of discontinuation of Humira® followed by a second course in patients treated successfully with the drug.

9. Labeling

Medication Guide

Patient labeling could help prevent serious adverse effects, and patients should be made aware of serious risks (relative to benefit). Information concerning the risk could affect patients' decision to use, or to continue use, of the product. Adalimumab labeling includes a "black box" warning describing the risk of serious infections including tuberculosis, invasive fungal infections, and other opportunistic infections. We determined that Humira® poses a serious and significant public health concern relating to the increased risk for serious infections, and that this risk required development of a medication guide under 21CFR 208.

Physician Labeling

I concur with the recommendations of the review team for the physician labeling. The final agreed upon text labeling will accompany the approval letter. The approval indication will be for "the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. Humira® should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician".

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