CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
sBLA 125057/110

PHARMACOLOGY REVIEW(S)
Pharmacology Toxicology Supervisor Memorandum

From: Paul C. Brown, Pharmacology Supervisor, Division of Dermatology and Dental Products

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

BLA 125057/110
Sponsor and/or agent: Abbott Laboratories
Drug:
Trade name: Humira
Generic name: adalimumab, recombinant human IgG1

Background:
The applicant is requesting approval of Humira in the treatment of moderate to severe chronic plaque psoriasis. This formulation is the same as that which is currently marketed. Adalimumab is approved for use in patients with rheumatoid arthritis, Crohn’s disease, ankylosing spondylitis and psoriatic arthritis. No new nonclinical studies have been submitted in this supplement.

Discussion:
As no new nonclinical studies were submitted with this supplement, the Division relied upon previous review of the nonclinical studies for the approval of adalimumab for rheumatoid arthritis.

Based on in vitro data, cynomolgus monkey was chosen as the relevant species for toxicologic testing of adalimumab. Binding of adalimumab to rodent TNFα occurs with much lower affinity than in primates. A 39-week toxicity study was conducted in cynomolgus monkeys with weekly intravenous administration of adalimumab at doses of 32, 82.9 and 214.8 mg/kg/week. In addition, two 4-week toxicity studies in cynomolgus monkeys were also conducted with weekly intravenous infusions of adalimumab. The initial 4 week study used doses of 60.8 and 179.6 mg/kg while the second final 4 week study used doses of 32, 70.9 and 157.2 mg/kg. In both the 4 week and 39 week studies effects included decreased cellularity of B-cells in splenic follicles. In the 39 week study involution of the thymus was noted at doses of 82.9 mg/kg and greater. The thymus effects were reversible after 20 weeks of recovery while the spleen effects were not entirely reversed. A NOAEL was not established in the 39 week monkey study since spleen effects were noted even at the 32 mg/kg dose.

It is noted that higher doses were used in the 39 week monkey study than were used in the 4 week monkey studies. The reason for this difference is not clear. However, the findings in the 4 week study may have been considered tolerable by the monkeys and so a higher dose may have been used in the 39 week study. While a NOAEL was not established in the 39 week monkey study, the observed effects appear to be related to the pharmacologic effects of adalimumab. These pharmacologic effects (immune suppression) appear to be responsible for most adverse effects observed from treatment.
with adalimumab. The doses used in the monkey studies are significantly higher than the human doses proposed by the sponsor, which are 80 mg administered SC at Week 0, followed by 40 mg every other week starting at Week 1. These would be approximately 0.5 to 1 mg/kg.

It is also noted that no studies specifically addressing carcinogenicity were conducted with adalimumab. TNFα inhibitors as a class have been labeled as having the potential to increase malignancies based on their pharmacologic activity. More recent findings from humans exposed to TNFα inhibitors have further suggested that this class carries an increased risk of malignancy. [b(4)]

At this time, additional animal studies are probably not necessary to characterize the potential hazards associated with adalimumab since the previously conducted animal studies and human use have already identified potential risks.

The nonclinical information that is described in the proposed labeling is the same as that as approved by the Division of Gastroenterology Products on 9/5/07 and is acceptable from a pharmacology/toxicology perspective.

Conclusion:
Adverse effects from the long term use of adalimumab will most likely be related to the immunosuppressive effects. This has been observed from previous human use as an increase in infections and an increased risk of some malignancies. Additional animal studies would probably not further characterize these effects. The risk may be best characterized from existing human use and the final approvability of this supplement will depend on assessment of these human data.
PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

BLA NUMBER: 125057
SERIAL NUMBER: 110
DATE RECEIVED BY CENTER: 3/23/07
PRODUCT: Humira
INTENDED CLINICAL POPULATION: Moderate to severe chronic plaque psoriasis
SPONSOR: Abbott Laboratories
DOCUMENTS REVIEWED: Electronic (All)
REVIEW DIVISION: Division of Dermatology and Dental Products (HFD-540)

PHARM/TOX REVIEWER: Carmen D. Booker, Ph.D.
PHARM/TOX SUPERVISOR: Paul Brown, Ph.D.
DIVISION DIRECTOR: Susan Walker, M.D.
PROJECT MANAGER: Tamika White

Date of review completion: November 8, 2007
TABLE OF CONTENTS

EXECUTIVE SUMMARY ........................................................................................................ 3

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW .................................................................... 5

2.6.1 INTRODUCTION AND DRUG HISTORY .................................................................. 5

2.6.2 PHARMACOLOGY .................................................................................................... 6

2.6.3 PHARMACOLOGY TABULATED SUMMARY ............................................................... 6

2.6.4 PHARMACOKINETICS/TOXICOKINETICS ............................................................... 6

2.6.5 PHARMACOKINETICS TABULATED SUMMARY ....................................................... 7

2.6.6 TOXICOLOGY .......................................................................................................... 7

2.6.7 TOXICOLOGY TABULATED SUMMARY ................................................................... 7

OVERALL CONCLUSIONS AND RECOMMENDATIONS ...................................................... 7
EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: The product is approvable with respect to nonclinical concerns.

B. Recommendation for nonclinical studies: None.

C. Recommendations on labeling: None.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Adalimumab has been the subject of prior approved BLAs and BLA supplements. No pharmacology and toxicology objections have been raised previously. No new toxicology studies have been conducted.

Based on in vitro data, cynomolgus monkey was chosen as the relevant species for toxicologic testing of adalimumab. A 39-week toxicity study was conducted in cynomolgus monkeys with weekly intravenous administration of adalimumab at doses up to 214.8 mg/kg/week. In addition, two 4-week toxicity studies in cynomolgus monkeys were also conducted with weekly intravenous infusions of adalimumab. Other nonclinical studies in monkeys, rabbits and mice were conducted. All these studies were reviewed in detail in the attached BLA pharmacology review written by Andrea Weir (2002).

Long-term animal studies of adalimumab have not been conducted to evaluate its carcinogenic potential or effect on fertility. No clastogenic or mutagenic effects of adalimumab were observed in the in vivo mouse micronucleus test or the Salmonella-Escherichia coli (Ames) assay, respectively. 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 100 mg/kg.

B. Pharmacologic activity

Adalimumab is a recombinant human IgG1 monoclonal antibody with human derived heavy and light chain variable regions and human IgG1: \( \kappa \) constant regions with specificity for TNF\( \alpha \). It is composed of 1330 amino acids and has a molecular weight of 148 kilodaltons.

Adalimumab binds to human TNF\( \alpha \) and blocks its interactions with the p55 and p75 cell surface TNF receptors. Molecular kinetics studies between adalimumab and rh TNF\( \alpha \) resulted in a \( K_D \) of 6.09 x \( 10^{-10} \) M. Adalimumab inhibited TNF\( \alpha \) binding in vitro resulting in an IC\( _{50} \) of 1.56 ± 0.12 e\( -10 \). In the presence of complement in vitro, adalimumab is also capable of lysing cells that express TNF on their surface. TNF is a naturally occurring cytokine involved in
inflammatory and normal immune responses. Adalimumab also affects other immune responses modulated by TNF including changes in adhesion molecules responsible for leukocyte migration.

*In vitro* studies using human whole blood demonstrated that adalimumab did not elicit the release of cytokines or cell surface markers. Adalimumab did not inhibit *in vitro* binding to 68 other receptors. Adalimumab demonstrated no mitogenicity when incubated with mitogens and murine splenic cells *in vitro*.

Adalimumab, administered by ip injection three times a week for 10 weeks, prevented the development of polyarthritis in several nonclinical studies in transgenic mice. Nonclinical safety pharmacology studies were also conducted by the sponsor and submitted with the original BLA. No safety pharmacology concerns were identified at that time. Several tissue cross-reactivity studies revealed that adalimumab binds to the vascular and intrinsic smooth muscle of multiple tissues. Adalimumab also reacted to filamentous structures in the cytoplasm of smooth muscle, cytoplasmic filamentous structures in other cells with contractile properties and capsular or extrinsic smooth muscle in the adrenal, testis and mammary gland.

C. Nonclinical safety issues relevant to clinical use

There are no nonclinical safety issues relevant to the clinical use of adalimumab.
2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

BLA number: 125057
Review number: 1
Sequence number/date: 110 / March 23, 2007
Information to sponsor: Yes ( ) No ( X )
Sponsor and/or agent: Abbott Laboratories
Manufacturer for drug substance: Abbott Laboratories

Reviewer name: Carmen D. Booker, Ph.D.
Division name: Division of Dermatology and Dental Products
HFD #: 540
Review completion date: November 8, 2007

Drug:
Trade name: Humira
Generic name: adalimumab, recombinant human IgG1
Molecular weight: 148 kDa

Relevant INDs/BLAs/DMFs: ☑
☑
☑ ☑ BLA 125057

Drug class: Anti-inflammatory

Intended clinical population: Moderate to severe chronic plaque psoriasis

Clinical formulation: This formulation is the same as that which is currently marketed. The manufacturer for this BLA, Abbott Laboratories, is the same manufacturer of the currently marketed drug product. Each single-use syringe (0.8 mL) contains 40 mg adalimumab, 4.93 mg sodium chloride, 0.69 mg monobasic sodium phosphate dehydrate, 1.22 mg dibasic sodium phosphate dehydrate, 0.24 mg sodium citrate, 1.04 mg citric acid monohydrate, 9.6 mg mannitol, 0.8 mg polysorbate 80 and Water for Injection, USP.

Route of administration: Subcutaneous

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of sBLA 125057 are owned by Abbott Laboratories or are data for which Abbott Laboratories has obtained a written right of reference. Any data or information described or referenced below from a previously approved application that Abbott Laboratories does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of sBLA 125057.
Previous human use: Adalimumab is approved for use in patients with rheumatoid arthritis, Crohn’s disease, ankylosing spondylitis and psoriatic arthritis.

Studies reviewed within this submission: None.

Studies not reviewed within this submission: None.

References:
Memorandum to file BLA 125057/0, from Andrea B Weir, Ph.D.; December 31, 2002.


2.6.2 PHARMACOLOGY

Adalimumab is a recombinant human IgG1 monoclonal antibody with human derived heavy and light chain variable regions and human IgG1:κ constant regions with specificity for TNFα. It is composed of 1330 amino acids and has a molecular weight of 148 kilodaltons.

Adalimumab binds to human TNFα and blocks its interactions with the p55 and p75 cell surface TNF receptors. Molecular kinetics studies between adalimumab and rh TNFα resulted in a KD of 6.09 x -10 M. Adalimumab inhibited TNFα binding in vitro resulting in an IC50 of 1.56 ± 0.12 e-10. In the presence of complement in vitro, adalimumab is also capable of lysing cells that express TNF on their surface. TNF is a naturally occurring cytokine involved in inflammatory and normal immune responses. Adalimumab also affects other immune responses modulated by TNF including changes in adhesion molecules responsible for leukocyte migration.

In vitro studies using human whole blood demonstrated that adalimumab did not elicit the release of cytokines or cell surface markers. Adalimumab did not inhibit in vitro binding to 68 other receptors. Adalimumab demonstrated no mitogenicity when incubated with mitogens and murine splenic cells in vitro.

Adalimumab, administered by ip injection three times a week for 10 weeks, prevented the development of polyarthritis in several nonclinical studies in transgenic mice. Nonclinical safety pharmacology studies were also conducted by the sponsor and submitted with the original BLA. No safety pharmacology concerns were identified at that time. Several tissue cross-reactivity studies revealed that adalimumab binds to the vascular and intrinsic smooth muscle of multiple tissues. Adalimumab also reacted to filamentous structures in the cytoplasm of smooth muscle, cytoplasmic filamentous structures in other cells with contractile properties and capsular or extrinsic smooth muscle in the adrenal, testis and mammary gland.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

See summary above.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS
Most pharmacokinetic studies with adalimumab were conducted in cynomolgus monkeys. Absolute bioavailability after subcutaneous administration was 96%. See attached review for a more detailed pharmacokinetic review.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY
See attached review.

2.6.6 TOXICOLOGY
Adalimumab has been the subject of prior approved BLAs and BLA supplements. No pharmacology and toxicology objections have been raised previously. No new toxicology studies have been conducted.

A 39-week toxicity study was conducted in cynomolgus monkeys with weekly intravenous administration of adalimumab at doses up to 214.8 mg/kg/week. In addition, two 4-week toxicity studies in cynomolgus monkeys were also conducted with weekly intravenous infusions of adalimumab. Other nonclinical studies in monkeys, rabbits and mice were conducted. All these studies were reviewed in detail in the attached original BLA pharmacology review written by Andrea Weir (2002).

Long-term animal studies of adalimumab have not been conducted to evaluate its carcinogenic potential or effect on fertility. No clastogenic or mutagenic effects of adalimumab were observed in the in vivo mouse micronucleus test or the Salmonella-Escherichia coli (Ames) assay, respectively. 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 100 mg/kg.

2.6.7 TOXICOLOGY TABULATED SUMMARY
See summary above.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Based on evaluation of previous pharmacology and toxicology reviews, the safety of adalimumab is adequately supported. There are no nonclinical safety issues relevant to the clinical use of adalimumab in patients with psoriasis. No objection is offered to approving this licensing application supplement.

Unresolved toxicology issues: None.

Recommendations: This sBLA is approvable in regard to pharmacologic and toxicologic concerns.

Suggested labeling: The labeling for this indication, with regard to nonclinical safety, will be the same as that previously approved for adalimumab.

Attachments:
Memorandum to file BLA 125057/0, from Andrea B Weir, Ph.D.; December 31, 2002.