National PBM Drug Monograph

Adalimumab (Humira ®)

VHA Pharmacy Benefits Management Strategic Healthcare Group
and Medical Advisory Panel

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient situation.

EXECUTIVE SUMMARY

Mode of Action:
Adalimumab is a human-derived recombinant IgG1 monoclonal antibody against tumor necrosis factor alpha (TNF-α). Adalimumab neutralizes and prevents the action of tumor necrosis factor (TNF), resulting in anti-inflammatory and antiproliferative activity.

FDA-Approved Indication:
Reduction of signs and symptoms and inhibition of the progression of structural damage in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs. Adalimumab can be used alone or in combination with MTX or other DMARDs.

Dosage and Route:
40 mg subcutaneously every other week; patients not receiving concurrent methotrexate may receive additional benefit by increasing dose to 40 mg once weekly.

Efficacy:
The pivotal trials of adalimumab assessed its safety and efficacy as monotherapy, in combination with MTX, and as add-on treatment to standard of care in clinical practice settings. One published clinical trial with results for adalimumab was available that looked at the safety and efficacy of adalimumab in comb with MTX in pts with active RA despite MTX treatment. The primary efficacy end-point was the American College of Rheumatology criteria for 20% improvement (ACR 20) at 24 weeks, which was found to be statistically superior for each adalimumab dosage group in combination with MTX compared to that of placebo plus MTX. However, the study was not intent to treat; mentioned use of a post hoc test to analyze the primary efficacy endpoint of the ACR 20, but did not define the statistical measure used prior to the post hoc; study was not powered to show a difference among adalimumab treatment groups; and multiple t-tests were done for each of the dosage groups for the secondary endpoints of ACR 50 and ACR 70. Abstracts are not published.

Safety:
The most common adverse drug reactions reported by patients in placebo-controlled trials were injection site reactions (erythema and/or itching, hemorrhage, pain or swelling) in 20% of patients treated with adalimumab compared to 14% of patients receiving placebo. The most serious adverse effects associated with adalimumab use are reports of serious infections, rare neurologic events, and malignancies. Adalimumab carries a black box warning stating a risk of infections that have been observed, specifically tuberculosis.

Comparison with Other Biologic Treatments for Rheumatoid Arthritis:
Clinical trials directly comparing adalimumab head-to-head with any other biologic DMARDS (etanercept, infliximab, and anakinra) are not available. Therefore, it is difficult to extrapolate superiority of one over the other. Adalimumab's advantages over its competitors lies in its infrequent dosing schedule (once every other week) and ease of administration (subcutaneous injection), which can affect patient compliance. Etanercept dosing involves subcutaneous injections twice a week or a recently approved once weekly schedule, while anakinra requires daily subcutaneous injections. Infliximab is dosed less frequently, but requires intravenous administration and nursing supervision.

Adverse event profiles appear to be similar among the biologic DMARD agents. Adalimumab, etanercept, and infliximab package labeling each contains a warning regarding the risk of tuberculosis infection and cautioning use in patients that have a history of tuberculosis or are predisposed to infection. Adalimumab and infliximab both have a black box warning, while etanercept has a bolded warning relaying the risk of tuberculosis.

Cost of adalimumab administered biweekly as per the manufacturer's product labeling is comparative with other available biologic agents. However, the potential remains for the use of adalimumab in the absence of methotrexate at a once-weekly dosing schedule, which would almost double the cost of therapy compared with a standard regimen of a competing agent.

Recommendations:
Adalimumab should remain non-formulary at both national and VISN levels with Criteria for Use. Use should be reserved for adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs as traditional DMARDs remain the gold standard for initial therapy. Also, there is a potential for dosing variability with adalimumab depending on the presence or absence of concurrent methotrexate therapy that is associated with a significant cost difference.

INTRODUCTION [1-11]

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder (affecting approximately 1% of the United States population) that frequently leads to a progressive destructive arthropathy causing deformities and disability. RA is characterized by pain, swelling, and stiffness of synovial joints. Tumor necrosis factor (TNF) is thought to play a role in the development and progression of rheumatoid arthritis. TNF levels are higher in patients with RA than in the general population.

RA is considered to be an autoimmune disease resulting from T-cell activation, releasing T-cell derived cytokines and stimulating activation of B-cells which facilitate multiple humoral responses. RA originates with an unidentified pathogen (i.e., an endogenous or exogenous antigen) that triggers a T-cell CD4+ - mediated immune response. The subsequent increased cellularity of the synovial tissue of affected joints allows antigen-activated CD4+ T-cells to infiltrate the synovium. These T-cells, in turn, activate monocytes, macrophages, and synovial fibroblasts to produce pro-inflammatory cytokines such as interleukins – 1 (IL-1) and – 6 (IL-6) and tumor necrosis factor-alpha (TNF-α). This chronic inflammation leads to synovial cell proliferation or pannus formation, ultimately leading to erosion of bone and cartilage, which characterize the hallmarks of joint damage.

Current drug therapy for RA management relies on varying combinations of NSAIDS, analgesics, corticosteroids, and disease-modifying anti-rheumatic drugs (DMARDs). DMARDs are slow-acting drugs that provide symptomatic relief and reduce the risk of progressive joint damage. DMARDs include sulfasalazine, methotrexate (MTX), gold preparations, penicillamine, azathioprine, hydroxychloroquine, leflunomide, cyclosporine, and biologic modifiers (e.g., TNF inhibitors). Most of the older antirheumatic agents often take several weeks or months to work. The mode of action of many DMARDs is not fully understood, but many appear to act by immune suppression. The recent introduction of new classes of therapeutic agents has contributed to major advances in the treatment of RA. The first TNF-α-blocking agents (infliximab and etanercept) received FDA approval for improving signs and symptoms of RA. These TNF-α blockers have demonstrated inhibition of progression of structural joint damage among patients with RA. In addition, the first IL-1 blocking agent (anakinra) has received approval for the reduction of signs and symptoms of RA and inhibition of progression of structural joint damage in RA as well.

Adalimumab is the newest anti-TNF monoclonal antibody for use in the treatment of RA. Adalimumab is the first fully human IgG1 monoclonal antibody against TNF-α. It does not contain non-human or artificially fused human sequences, suggesting a low propensity for immunogenicity. The FDA approved this biological agent on December 31, 2002 for the reduction in signs and symptoms and the inhibition of progression of structural damage in adult patients with moderately to severely active RA who have responded inadequately to one or more DMARDs.

PHARMACOLOGY/PHARMACOKINETICS [2, 10, 12-14]

Adalimumab is a human-derived recombinant IgG1 monoclonal antibody engineered by recombinant deoxyribonucleic acid (DNA) technology. Adalimumab binds to TNF-α, a naturally occurring cytokine involved in normal immune and inflammatory responses, and blocks its interaction with the p55 and p75 cell-surface TNF receptors. It also lyses TNF-expressing cells in vitro in the presence of complement.

TNF-α, present in excess in the synovial fluid of patients with RA as an overproduction by macrophages, mediates pathological inflammation and joint destruction as manifested by the disease. Adalimumab does not bind to or inactivate TNF-β (also known as lymphotoxin). However, adalimumab modulates various biological responses responsible for leukocyte migration occurring consequent to the TNF-α activity: endothelial leukocyte adhesion molecule (ELAM-1), vascular cell adhesion molecule (VCAM-1), intracellular adhesion molecule (ICAM-1).

Table 1: **Pharmacokinetics of Adalimumab**

C max *(after a single 40mg subcutaneous dose)*	4.7 ±1.6 ug/mL
T max *(after a single 40mg subcutaneous dose)*	131 ± 56 hours
Bioavailability *(after a single 40mg subcutaneous dose)*	64%
Systemic Clearance *(after a single intravenous dose – range 0.5-10.0mg/kg)*	12 mL/hr
Volume of Distribution *(after a single intravenous dose – range 0.5-10.0mg/kg)*	4.7-6.0 L
Half-life *(after a single intravenous dose – range 0.5-10.0mg/kg)*	2 weeks, ranging from 10-20 days
Trough levels (steady state) *(after a single intravenous dose – range 0.5-10.0mg/kg)*	5 ug/mL without MTX 8-9 ug/mL with MTX

FDA APPROVED INDICATION(S) AND OFF-LABEL USES [2]

Adalimumab's current FDA-approved indication is for the reduction of signs and symptoms and the inhibition of the progression of structural damage in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs. Adalimumab can be used alone or in combination with MTX or other DMARDs.

CURRENT VA NATIONAL FORMULARY STATUS

Adalimumab (Humira): Non-Formulary
Anakinra (Kineret): Non-Formulary
Etanercept (Enbrel): Non-Formulary with criteria
Infliximab (Remicade): Non-Formulary with criteria

DOSAGE AND ADMINISTRATION [2]

The recommended dose of adalimumab is 40mg given every other week subcutaneously (SQ). MTX, glucocorticoids, salicylates, NSAIDs, analgesics, or other DMARDs may be continued during treatment with adalimumab. In patients not receiving MTX concomitantly, additional benefit may be obtained by increasing the frequency to weekly dosing.

Adalimumab is intended for use under the guidance and supervision of a physician. Patients may self-inject adalimumab according to the directions provided in the Patient Information Leaflet if they have received proper training in injection technique, their physician allows the self-injection, and the appropriate medical follow-up is scheduled. Injection sites should be rotated and injections should never be given into areas where skin is tender, bruised, red, or hard.

Adalimumab is supplied as pre-filled 1-mL syringes with 27-gauge, ½-inch needles containing 40mg of adalimumab. The drug must be protected from light and refrigerated at 2° - 8° Celsius.

ADVERSE EFFECTS (SAFETY DATA) [2, 15]

Table 2 reflects adverse events reported by ≥ 5% of patients treated with adalimumab during placebo-controlled RA studies as per the package insert.

Table 2

Percent (%) of RA Patients Reporting Adverse Events		
Adverse Event	Adalimumab 40 mg subcutaneous Every Other Week (N=705)	Placebo (N=690)
RESPIRATORY		
Upper respiratory infection	17	13
Sinusitis	11	9
Flu syndrome	7	6
GASTROINTESTINAL		
Nausea	9	8
Abdominal pain	7	4
LABORATORY TESTS		
Laboratory test abnormal	8	7
Hypercholesterolemia	6	4
Hyperlipidemia	7	5
Hematuria	5	4
Alkaline phosphatase increased	5	3
OTHER		
Injection site pain	12	12
Headache	12	8
Rash	12	6
Accidental Injury	10	8
Injection site reaction	8	1
Back pain	6	4
Urinary tract Infection	8	5
Hypertension	5	3

The most common adverse drug reactions reported by patients in placebo-controlled trials were injection site reactions, occurring in 20% of patients treated with adalimumab compared to 14% of patients receiving placebo. These reactions involved erythema and/or itching, hemorrhage, pain or swelling, and generally did not lead to cessation of treatment.

The most serious adverse reactions include serious infections, neurologic events, and malignancies.

- Infections
  Adalimumab carries a black box warning stating a risk of infections that have been observed, specifically tuberculosis. Per the package insert, 13 cases of tuberculosis have been reported in association with the administration of adalimumab in clinical trials.

- Neurologic Events
  Data is limited to the package insert, which states that adalimumab has been associated with rare cases of worsening of clinical symptoms and/or radiographic evidence of demylinating disease.

- Malignancy
  Various malignancies have occurred in patients treated with adalimumab in clinical trials. Out of 2468 patients, 48 malignancies were reported. Ten of these patients presented with lymphoma. Other malignancies observed include breast, colon-rectum, uterine-cervical, prostate, melanoma, gall bladder-bile ducts, and other carcinomas not specified.

Even though adalimumab is a fully human monoclonal antibody, approximately 5% (58 of 1062) developed low-titer antibodies to the agent at least once during therapy. Patients on adalimumab monotherapy had a higher rate of development of antibodies than patients receiving adalimumab in combination with methotrexate (12% vs. 1%). Patients receiving adalimumab monotherapy every other week may develop antibodies more often than those on a weekly schedule. Long-term immunogenicity data is not known.

A safety trial of adalimumab performed by Schiff et al. assessed the safety of adalimumab 40mg subcutaneously every other week added to pre-existing antirheumatic treatment (consisting of DMARDs, corticosteroids, and NSAIDs). Results reported an overall incidence of adverse events of 86.5% versus 82.7% for the adalimumab and placebo groups, respectively. Serious adverse events occurred in 5.3% of adalimumab patients versus 6.9% receiving placebo; infections occurred in 51.9% versus 49.4% of patients receiving adalimumab compared to placebo, respectively; and serious infections (requiring intravenous antibiotics or hospitalization) occurred in 1.3% of adalimumab patients compared to 6.9% receiving placebo. Patient withdrawal due to an adverse event reached 2.8% for patients in the adalimumab group compared with 2.2% in the placebo group. Injection site reactions were increased in the adalimumab arm (8.8% vs.0.6% with placebo).

PRECAUTIONS/CONTRAINDICATIONS [2]

Adalimumab is contraindicated in patients with prior hypersensitivity to adalimumab or any component of its formulation.

Major warnings for use include the association of adalimumab with serious infections and sepsis, including fatalities. Patients on concomitant immunosuppressive treatment could have an increased risk of developing infections. Tuberculosis and opportunistic fungal infections have been observed in patients treated with adalimumab. Therapy should not be initiated in patients with active infections (chronic or localized). Development of new infections while receiving therapy with adalimumab necessitates close monitoring. Adalimumab should be discontinued if a patient develops a serious infection. Caution is needed when considering initiation of adalimumab in patients with a history of recurrent infection, in patients with underlying conditions predisposing to infections, or in patients geographically located where tuberculosis and histoplasmosis are widespread.

DRUG INTERACTIONS [2]

Methotrexate reduced adalimumab clearance after single and multiple dosing by 29% and 44%, respectively. Adalimumab mean steady-state concentrations are 5ug/mL without concomitant methotrexate therapy and 8-9 ug/mL with concomitant methotrexate therapy. No dosage adjustments are needed for either adalimumab or methotrexate.

EFFICACY MEASURES [1, 16-18]

The primary measurement used to determine the efficacy of adalimumab in the treatment of rheumatoid arthritis (RA) in published clinical trials is the American College of Rheumatology Criteria for Response (ACR), which is defined as:

- ≥20% improvement in Tender Joint Count
- ≥20% improvement in Swollen Joint Count
- ≥20% improvement in 3 of the following 5:
  - Patient pain assessment
  - Patient global assessment

- Physician global assessment
- Patient self-assessed disability (disability index of the Health Assessment Questionnaire [HAQ])
- Acute phase reactant (C-reactive protein [CRP])

Additionally, radiographic changes were evaluated using the modified Sharp method for x-ray scoring, where radiographs of hands, wrists, and feet are scored.

- 46 joints are scored for erosions on a 6-point scale. A score of "0" indicates no new erosion and no worsening of an existing erosion, while each point increase indicates occurrence of a new erosion or 20% worsening of an existing erosion.
- 42 joints are scored for narrowing on a 5-point scale. A score of "0" indicates no narrowing; "1" indicates minimal narrowing; "2" indicates loss of 50% of the joint space; "3" indicates loss of 75% of the joint space; and "4" indicates complete loss of the joint space.

Scores for erosions and joint space narrowing are summed to give a total Sharp score.

CLINICAL TRIALS [19-24]

Citation: Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti-tumor necrosis factor-α monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate. The ARMADA Trial. Arthritis & Rheum 2003; 48(1): 35-45.	
Study Goal	To evaluate the efficacy and safety of adalimumab administered subcutaneously every other week to patients with active RA despite long-term treatment with methotrexate
Methods	**Study Design** - Type of Study 24-week randomized, double-blind, placebo-controlled trial of adalimumab with concomitant methotrexate treatment performed at 35 sites throughout the United States and Canada. - Treatment Groups Placebo or adalimumab 20mg, 40mg,or 80mg subcutaneously every other week as two injections of 1.6mL per injection. Patients were instructed in self-injection techniques. - Randomization Using a block size of 8. Only centers that enrolled multiples of 8 patients would have equal numbers of patients in each treatment group. - Efficacy Measures Primary efficacy end point: ACR 20 response Secondary efficacy endpoints: ACR 50 and ACR 70 response rates; tender joint count (TJC); swollen joint count (SJC); patient's assessment of pain; patient's global assessment of disease activity; physician's global assessment of disease activity; the Disability Index of the Health Assessment Questionnaire (HAQ); serum levels of C-reactive protein; Short Form 36 (SF-36); Functional Assessment of Chronic Illness Therapy (FACIT); serum concentrations of pro-matrix metalloproteinase 1 (proMMP-1) and proMMP-3 - Safety Assessments Adverse events reported by patients, serum levels of antiadalimumab antibodies, antinuclear antibodies (ANA), and anti-double-stranded DNA (anti-dsDNA) antibodies **Data Analysis** - Power Analysis Effect size: 35% in ACR 20 response rates Power: 90% Level of significance: $P \leq 0.05$ The study was not powered to show a difference among adalimumab treatment groups. - Statistical Tests Efficacy end points were analyzed on an intent-to-treat basis and included all patients who received at least one dose of study drug (adalimumab or placebo). Differences in the percentage of patients achieving an ACR 20 response at week 24 were compared between each of the adalimumab dosage groups and the placebo group by use of Dunnett's test. Differences in the percentages of patient achieving ACR 50 and ACR 70 responses at week 24 were compared between each of the adalimumab dosage groups and the placebo group by use of an unadjusted t-test without correction for multiple comparisons. Differences in the change from baseline to the last observation carried forward (LOCF) to week 24 in other secondary efficacy end points were compared between each of the adalimumab dosage groups and the placebo group by use of ANCOVA, with baseline as the covariate and without correction for multiple comparisons.

	Adverse events were compared between the adalimumab and placebo groups by use of Pearson's chi-square test without correction for multiple comparisons. Adverse events also analyzed by the total number of patients experiencing a particular adverse event per total years of treatment (number of patients/patient year).
Criteria	**Inclusion Criteria** Age ≥18 years; RA diagnosed according to the 1987 revised criteria of the American College of Rheumatology (ACR); active disease, defined as the presence of at least 9 tender joints (of 68 joints evaluated) and 6 swollen joints (of 66 joints evaluated); methotrexate treatment for a minimum of 6 months; stable weekly dose of methotrexate (12.5-25 mg, or 10 mg if intolerant to higher doses) for at least 4 weeks before entering the study; must have failed treatment with at least 1 DMARD besides methotrexate, but no more than 4 DMARDs. **Exclusion Criteria** Standard exclusion criteria used in trials of other biologics in patients with RA; anti-CD4 therapy or TNF-α antagonists; history of active listeriosis or mycobacterial infection; major infection requiring hospitalization or treatment with intravenous antibiotics within 30 days or oral antibiotics within 14 days prior to screening.
Results	Total of 271 patients met entry criteria. **Percent patients with ACR 20, ACR50, and ACR 70 responses at week 24**

OUTCOME MEASURES	**ACR 20%** *P**	**ACR 50%** *P***	**ACR 70%** *P***
DOSE			
Placebo + MTX (n=62)	**14.5**	**8.1**	**4.8**
Adalimumab 20mg every other week + MTX (n=69)	**47.8** *<0.001*	**31.9** *0.003*	**10.1** *NS*
Adalimumab 40mg every other week + MTX (n=67)	**62.7** *<0.001*	**55.2** *<0.001*	**26.9** *<0.001*
Adalimumab 80mg every other week + MTX (n=73)	**65.8** *<0.001*	**42.5** *<0.001*	**19.2** *0.020*

* Adalimumab vs. placebo, by Dunnett's test; statistical significance was set at P≤ 0.05.
** Adalimumab vs. placebo, by unadjusted t-test; statistical significance was set at P ≤ 0.05.
NS – Not significant

ADVERSE EVENTS	Placebo (n=62)	Adalimumab 20mg Every other week (n=69)	Adalimumab 40mg Every other week (n=67)	Adalimumab 80mg Every other week (n=73)
Rhinitis # of patients (%) # per patient-year^	12 (19.4) 0.57	16 (23.2) 0.58	17 (25.4) 0.60	17 (23.3) 0.54
Upper respiratory tract infection # of patients (%) # per patient-year^	6 (9.7) 0.29	14 (20.3) 0.51	10 (14.9) 0.36	16 (21.9) 0.51
Nausea # of patients (%) # per patient-year^	4 (6.5) 0.19	13 (18.8)* 0.47	3 (4.5) 0.11	7 (9.6) 0.22
Flu syndrome # of patients (%) # per patient-year^	5 (8.1) 0.24	8 (11.6) 0.29	10 (14.9) 0.36	5 (6.8) 0.16
Headache # of patients (%) # per patient-year^	6 (9.7) 0.29	7 (10.1) 0.26	4 (6.0) 0.14	21 (10.0) 0.32
Injection site pain** # of patients (%) # per patient-year^	2 (3.2) 0.10	6 (8.7) 0.22	7 (10.4) 0.25	8 (11.0) 0.26
Accidental Injury # of patients (%) # per patient-year^	7 (11.3) 0.33	4 (5.8) 0.15	10 (14.9) 0.36	6 (8.2) 0.19
Diarrhea # of patients (%) # per patient-year^	5 (8.1) 0.24	6 (8.7) 0.21	7 (10.4) 0.25	4 (5.5) 0.13
Rash # of patients (%) # per patient-year^	3 (4.8) 0.14	7 (10.1) 0.26	3 (4.5) 0.11	5 (6.8) 0.16
Injection site reaction** # of patients (%) # per patient-year^	0 0	3 (4.3) 0.11	1 (1.5) 0.04	8 (11.0)* 0.26
Dizziness # of patients (%) # per patient-year^	1 (1.6) 0.05	8 (11.6)* 0.29	1 (3.0) 0.7	1 (1.4) 0.03

^ # per patient-year = the # of patients experiencing the particular adverse event per total years of treatment.
* $P < 0.05$ vs. placebo, by Pearson's chi-square test without correction for multiple comparisons.
** Both categorized as "injection site reaction" according to the Hoechst Adverse Reaction Terminology System (HARTS) body system coding dictionary.

Three patients tested positive for anti-adalimumab antibodies (one taking placebo, one taking 20 mg of adalimumab, and one taking 80 mg of adalimumab).

At week 24, 18 of the 162 adalimumab-treated patients (11.1%) and 3 of the 49 placebo-treated patients (6.1%) who were negative for the presence of ANA at baseline converted to ANA positive. The difference between treatment groups was not statistically significant.

At week 24, 8 of the 204 adalimumab treated patients (3.9%) but none of the placebo-treated patients who were negative for the presence of anti-dsDNA antibodies at baseline converted to anti-dsDNA positive.

Conclusions	The addition of adalimumab at a dosage of 20mg, 40mg, or 80mg administered subcutaneously every other week to long-term methotrexate therapy in patients with active RA provided significant, rapid, and sustained improvement in disease activity over 24 weeks compared with methotrexate plus placebo.

Critique	76.8% female patients; overall mean age was approximately 55 years. The study was not powered to show a difference among adalimumab treatment groups. P-values are reported without adjustments for multiple comparisons. Study funded by Abbott Laboratories and Knoll Pharmaceuticals. Five of the authors received honoraria from Abbott Laboratories and Knoll Pharmaceuticals.

Citation: Kavanaugh AF, Weinblatt M, Keystone E, et al. The ARMADA Trial: 12-month efficacy and safety of combination therapy with adalimumab (D2E7), the first fully human anti-TNF monoclonal antibody, and methotrexate (MTX) in patients with active rheumatoid arthritis. Abstract presented at: The European Congress of Rheumatology, June 12-15, 2002, Stockholm, Sweden.

Study Goal	To evaluate the efficacy and safety of adalimumab administered subcutaneously every other week to patients with active RA despite long-term treatment with methotrexate for an additional 6 months, for a total of 12-months (including the initial double-blind portion of the trial).
Methods	**Study Design** - Type of Study Open label continuation period of an additional 6 months for the ARMADA trial. After completing the double-blind portion of the trial, 250 patients entered the open-label study. - Treatment Groups All patients received 40mg of adalimumab subcutaneously every other week in combination with methotrexate - Efficacy Measures Primary efficacy end point: ACR 20 response Secondary efficacy endpoints: ACR 50 and ACR 70 response rates; tender joint count (TJC); swollen joint count (SJC) - Safety Assessments Adverse events reported by patients **Data Analysis** Not reported/discussed.
Criteria	Completion of the initial double-blind study portion.
Results	• 250 patients entered the open label study • 231 patients completed (8 withdrew for adverse events; 11 withdrew for lack of efficacy or administrative reasons) • Results are presented as compiled results for 12 months (including results from the initial double-blinded study portion). Percent patients per ACR response category DOSE / ACR 20% / ACR 50% / ACR 70% Adalimumab 40mg every other week + MTX / 71.2 % / 50.8% / 26.0% • Swollen Joint Count (change from baseline): -11.2 • Tender Joint Count (change from baseline): -18.3 • # of serious adverse events: 0.11 per patient-year (for the second 6 months only) • Rate of serious infections (requiring IV antibiotics or hospitalization): 0.03 per patient-year (for the second 6 months only) • No cases of tuberculosis were seen
Conclusions	Adalimumab therapy added to MTX partial responders continued to demonstrate sustained clinical efficacy throughout one year. Adalimumab plus MTX therapy was safe and well tolerated throughout the course of this study.

Critique	Study is open label. As this trial is currently only available in abstract form, final conclusions cannot be drawn. 75.6 % female patients; mean age approximately 55.1 years. Eligibility, statistical methods, and p-values are not reported/discussed. Endpoints are combined with initial double-blinded portion of the study. Adverse events are not explained in detail.

Citation: van de Putte LB Atkins C, Malaise M, et al. Efficacy and safety of adalimumab (D2E7), the first fully human anti-TNF monoclonal antibody, in patients with rheumatoid arthritis who failed previous DMARD therapy: 6-month results from a phase III study. Abstract presented at: The European Congress of Rheumatology, June 12-15, 2002, Stockholm, Sweden.

Study Goal

To assess the safety and efficacy of adalimumab in patients with long-standing rheumatoid arthritis (RA) who had failed at least one traditional disease-modifying antirheumatic drug (DMARD)

Methods

Study Design

- Type of Study
Phase III, double-blind, randomized, placebo-controlled monotherapy study

- Treatment Groups
Patients were randomized to adalimumab 20 mg or 40 mg subcutaneously every other week or weekly or to placebo

- Length of Study
4-week washout periods, during which all DMARDs were discontinued, followed by a 26-week, placebo-controlled period.

- Efficacy Measures
ACR 20, ACR 50, and ACR 70 response rates; tender joint count (TJC); swollen joint count (SJC)

- Safety Assessments
Adverse events reported by patients

Data Analysis

Not reported/discussed.

Criteria

Not reported/discussed.

Results

544 patients were randomized to one of five treatment groups

Outcome measures per treatment group

	Placebo (n=110)	Adalimumab 20mg Every other week (n=106)	Adalimumab 20mg Every week (n=112)	Adalimumab 40mg Every other week (n=113)	Adalimumab 40mg Every week (n=103)
ACR 20%	19.1	35.8[a]	39.3[a]	46.0[a]	53.4[abc]
ACR 50%	8.2	18.9[a]	20.5[a]	22.1[a]	35.0[abcd]
ACR 70%	1.8	8.5[a]	9.8[a]	12.4[a]	18.4[ab]
TJC % Decrease	-13.2	-39.1[a]	-46.9[a]	-45.5[a]	-56.8[a]
SJC % Decrease	-14.9	-29.4[a]	-44.9[a]	-44.1[a]	-50.9[a]

[a]P<0.05 vs. placebo; [b]P<0.05 vs. 20 mg every other week; [c]P<0.05 vs. 20 mg every week; [d]P<0.05 vs. 40 mg every other week
*Median

	The most common adverse events were injection site reaction (9.7%), rash (9.4%), and headache (9.4%).
Conclusion	Adalimumab administered alone in RA patients demonstrated rapid, consistent efficacy in treating the signs and symptoms of RA. Adalimumab was safe and well tolerated at all dosages tested.
Critique	As this trial is currently only available in abstract form, final conclusions cannot be drawn. 77% female patients; mean age approximately 53 years. Eligibility and statistical methods are not discussed.

Citation: Keystone E, Kavanaugh AF, Sharp J, et al. Adalimumab (D2E7), a fully human anti-TNF-α monoclonal antibody, inhibits the progression of structural joint damage in patients with active RA despite concomitant methotrexate therapy. Abstract presented at: The 66th Annual Meeting of the American College of Rheumatology, October 24-29, 2002, New Orleans, LA.

Study Goal: To evaluate the safety, efficacy, and radiographic outcome of adalimumab in patients with active RA who were incomplete responders to MTX therapy

Methods:

Study Design

- Type of Study
52-week, double blind, randomized, placebo-controlled trial

- Treatment Groups
Randomly assigned to receive subcutaneous adalimumab 20mg weekly, 40 mg every other week, with placebo on alternate weeks, or placebo weekly.

- Efficacy Measures
Modified Sharp x-ray score; erosion score; joint space narrowing score

- Safety Assessments
Adverse Events reported by patients

Data Analysis

Not reported/discussed.

Criteria:

Inclusion Criteria

Patients with RA on stable doses of MTX.

Exclusion Criteria

Not reported/discussed.

Results:

619 patients were randomized

Radiographic changes per treatment group

ENDPOINT (Mean score of 2 readers)	Adalimumab 20mg Weekly (n=212)	Adalimumab 40mg Every other week (n=207)	Placebo (n=200)
Modified Sharp x-ray score			
Mean baseline score	66.4	72.1	66.4
Mean change at week 52	0.8*	0.1*	2.7
Median change at week 52	0.0*	0.0*	1.0
Erosion score			
Mean baseline score	36.7	41.4	37.2
Mean change at week 52	0.4*	0.0*	1.7
Joint space narrowing score			
Mean baseline score	29.7	30.7	29.2
Mean change at week 52	0.5	0.1*	1.1

	**P≤0.001 versus placebo* Percent patients with no new erosions at week 52 Adalimumab 20mg Weekly (n=212): 57.9%, *P≤0.05* Adalimumab 40mg Every other week (n=207): 61.8%, *P≤0.001* Placebo (n=200): 46.0% Percent patients with ACR responses at week 52 *P≤0.01* Most frequently reported adverse events in adalimumab group (reported as % patients):

	Adalimumab 20mg Weekly (n=212)	Adalimumab 40mg Every other week (n=207)	Placebo (n=200)
ACR 20%	54.7%	58.9%	24.0%
ACR 50%	37.7%	41.5%	9.5%
ACR 70%	20.8%	23.2%	4.5%

	Adalimumab (all doses)	Placebo
Injection site reactions	22.9%	23.5%
Upper respiratory infections	19.6%	13.5%
Rhinitis	16.9%	16.5%
Sinusitis	15.3%	13.0%

Conclusions	Adalimumab given subcutaneously weekly (20mg) or every other week (40 mg) with concomitant MTX significantly inhibited progression of structural joint damage and improved signs and symptoms of RA in patients who previously were incomplete responders to MTX. The 2 adalimumab dosages were comparably effective and well tolerated.
Critique	As this trial is currently only available in abstract form, final conclusions cannot be drawn. 77% female patients; mean age approximately 57 years. Eligibility and statistical methods are not discussed. Data non-normal. Study funded by Abbott Laboratories.

Citation: Furst DE, Fleischmann R, Birbara C, et al. Efficacy of adalimumab (D2E7), a fully human anti-TNF monoclonal antibody, administered to rheumatoid arthritis patients in combination with other antirheumatic therapy in the STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis) Trial. Abstract presented at: The European Congress of Rheumatology, June 12-15, 2002, Stockholm, Sweden.	
Study Goals	To determine the safety and efficacy of the combination of adalimumab and standard antirheumatic therapy
Methods	**Study Design** -Type of Study 24-week, double-blind, randomized, placebo-controlled trial -Treatment Groups Adalimumab 40mg subcutaneously every other week or placebo added to pre-existing antirheumatic therapy

<table>
<tr><td></td><td>-Efficacy Measures
ACR 20, ACR 50, and ACR 70 response rates; tender joint count (TJC); swollen joint count (SJC); HAQ

<u>Data Analysis</u>

Not reported/discussed.</td></tr>
<tr><td>Criteria</td><td>Patients with active RA.</td></tr>
<tr><td>Results</td><td>636 patients were randomized to adalimumab 40 mg subcutaneously every other week or placebo

Percent patients per ACR response category
<table>
<tr><td></td><td>ACR 20%</td><td>ACR 50%</td><td>ACR 70%</td></tr>
<tr><td>Adalimumab 40mg subcutaneously every other week + standard of care (n=318)</td><td>51.9%</td><td>28.9%</td><td>14.8%</td></tr>
<tr><td>Placebo + standard of care (n=318)</td><td>34.6%</td><td>11.3%</td><td>3.5%</td></tr>
</table>
P≤0.001

Decrease from baseline of tender joint counts (TJC), swollen joint counts (SJC), and HAQ points per group
<table>
<tr><td></td><td>TJC*</td><td>SJC*</td><td>HAQ*</td></tr>
<tr><td>Adalimumab 40mg subcutaneously every other week + standard of care (n=318)</td><td>14.9</td><td>10.2</td><td>0.5</td></tr>
<tr><td>Placebo + standard of care (n=318)</td><td>10.2</td><td>6.5</td><td>0.2</td></tr>
</table>
P≤0.001
* Decrease from baseline

Response rates broken down by concomitant DMARD therapy
<table>
<tr><td></td><td>ACR 20%</td><td>ACR 50%</td></tr>
<tr><td>Adalimumab + 0 DMARDs</td><td>49.1%</td><td>26.3%</td></tr>
<tr><td>Adalimumab + 1 DMARDs</td><td>55.4%</td><td>30.6%</td></tr>
<tr><td>Adalimumab + 2-4 DMARDs</td><td>49.3%</td><td>26.6%</td></tr>
<tr><td>Placebo + 0 DMARDs</td><td>30.8%</td><td>7.7%</td></tr>
<tr><td>Placebo + 1 DMARDs</td><td>39.1%</td><td>12.4%</td></tr>
<tr><td>Placebo + 2-4 DMARDs</td><td>29.9%</td><td>11.3%</td></tr>
</table></td></tr>
<tr><td>Conclusions</td><td>This study demonstrated that adalimumab significantly improved the signs and symptoms of RA when added to standard antirheumatic care in a heterogeneous group of RA patients on multiple different therapeutic regimens. Adalimumab showed improved efficacy for patients when administered without any additional DMARDs, as well as on the background of one or multiple DMARD combinations.</td></tr>
<tr><td>Critique</td><td>As this trial is currently only available in abstract form, final conclusions cannot be drawn. 79.4% female patients; mean age approximately 55 years. Eligibility and statistical methods are not discussed.</td></tr>
</table>

<table>
<tr><td colspan="2">Citation: Burmester GR, van de Putte LB, Rau R, et al. 2-Year experience with adalimumab (D2E7), the first fully human anti-TNF monoclonal antibody, in patients with DMARD-refractory rheumatoid arthritis. Abstract presented at: The European Congress of Rheumatology, June 12-15, 2002, Stockholm, Sweden.</td></tr>
<tr><td>Study Goals</td><td>To assess the safety and efficacy of monotherapy with adalimumab 40mg administered subcutaneously on a weekly basis during a second year of treatment in patients with long-standing RA who had failed at least one disease-modifying antirheumatic drug (DMARD)</td></tr>
<tr><td>Methods</td><td><u>Study Design</u>

- Type of Study
12-month, open-label, continuation period (III) or a 2-year phase II trial. [Period I consisted of a 12-week, placebo-controlled, double-blind, multidose (20mg, 40mg, 80mg weekly) period and was followed by period II, which was a 40-week, double-blind, continuation period during which patients randomized to</td></tr>
</table>

<table>
<tr><td></td><td>placebo during period I were switched to adalimumab 40 mg.]

-Treatment Groups
All patients received adalimumab 40mg subcutaneously per week.

-Efficacy Measures
ACR 20, ACR 50, and ACR 70 response rates; tender joint count (TJC); swollen joint count (SJC)

<u>Data Analysis</u>

Not reported/discussed.</td></tr>
<tr><td>Criteria</td><td>Not reported/discussed.</td></tr>
<tr><td>Results</td><td>229 patients entered the open-label continuation period (III)
205 patients completed the open-label treatment with adalimumab during period III

Percent pateints on adalimumab 40mg subcutaneously every week achieving each ACR response category per year
<table>
<tr><td></td><td>ACR 20%</td><td>ACR 50%</td><td>ACR 70%</td></tr>
<tr><td>Year 2 (Period III – Open label)</td><td>76</td><td>52</td><td>24</td></tr>
<tr><td>Year 1 (Periods I & II)</td><td>79</td><td>46</td><td>21</td></tr>
</table></td></tr>
<tr><td>Conclusions</td><td>In DMARD-refractory RA patients, adalimumab continues to show a high level of clinical efficacy after 2 years. Adalimumab therapy was safe and well tolerated throughout the course of this study. The vast majority of patients who entered the second year of treatment chose to remain on adalimumab.</td></tr>
<tr><td>Critique</td><td>Study is open-label. As this trial is currently only available in abstract form, final conclusions cannot be drawn. 80% female patients; mean age approximately 59 years. Eligibility and statistical methods are not discussed. P-values are not reported. Adverse events are not reported in detail.</td></tr>
</table>

ACQUISITION COSTS

** Costs as reported below reflect current pricing only. Please refer to the PBM website (vaww.pbm.med.va.gov or www.vapbm.org) for updated cost information.*

Product	Dose	Schedule	Cost per dispensing unit	Cost/ Patient /Year ($)
Adalimumab (Humira ®)	40 mg	Every other week	$687.74/2 single-use syringes (40mg/1ml syringe)	$8,940.62
Adalimumab (Humira ®)	40 mg	Weekly	$687.74/2 single-use syringes (40mg/1ml syringe)	$17,881.24
Anakinra (Kineret®)	100 mg	Once daily	$166.77/7 single-use syringes (100mg/1ml syringe)	$8,672.04
Etanercept (Enbrel®)	25mg	Twice weekly	$360.06/4 SDV (25mg/vial)	$9,361.56
Etanercept (Enbrel®)	50mg	Once weekly	$360.06/4 SDV (25mg/vial)	$9,361.56
Infliximab (Remicade®) +	3 mg/kg	Once every 8 weeks	$389.32/20ml vial (100mg/20ml vial)	<70kg $7,007.76 - $10,511.64 >70kg $10,511.64 - $14,015.52
Infliximab (Remicade®) +	10 mg/kg	Once every 8 weeks	$389.32/20ml vial (100mg/20ml vial)	<70kg $21,023.28 - $24,527.16 >70kg $24,527.16 - $28,031.04
Methotrexate‡	15 mg	Weekly	$1.50/6-2.5 mg tabs	$ 78.00

SDV = single dose vials

\+ Costs include infusion at weeks 0, 2,6,14,22,30,38,46,54
3mg/kg <70kg 2-3 vials, >70kg 3-4 vials
10mg/kg <70kg 6-7 vials, >70kg 7- 8 vials

‡ Methotrexate included to calculate combination therapy costs

Conclusions [25-31]

Efficacy and safety of adalimumab was assessed in four pivotal clinical trials (in combination with MTX, as monotherapy, or with other DMARDs) in patients with moderately to severely active RA. One of these clinical trials, the ARMADA Trial, has been published in a peer-reviewed journal. The other data is only available as abstracts presented at various meetings, such as the 66th Annual Meeting of the American College of Rheumatology and the European Congress of Rheumatology. Baseline characteristics of most of the participants in these clinical trials were female gender, disease duration of 10-12 years, and had a mean age range of 53-57 years. Generalizability of these results to a predominantly male, elderly population, such as VA patients is questionable.

Adalimumab is the third immunobiological agent targeted at TNF-α. However, in the absence of clinical trials that directly compare adalimumab head-to-head with other biologic DMARDS, it is difficult to extrapolate superiority of one agent over the other and predict adalimumab's place alongside the two other FDA-approved anti-TNF-α agents, etanercept and infliximab, as well as the IL-1 receptor antagonist, anakinra. Adalimumab's advantages over its competitors lie in its infrequent dosing schedule (once every other week) and ease of administration (subcutaneous injection), which can affect patient compliance. On the other hand, etanercept dosing involves subcutaneous injections twice a week or a recently approved once weekly schedule, while anakinra requires daily subcutaneous injections. In addition, infliximab is dosed less frequently, but requires intravenous administration and nursing supervision. Adalimumab has been administered with various DMARD therapies and no significant drug interactions have been noticed.

Adverse event profiles appear to be similar among the biologic DMARD agents. Adalimumab, etanercept, and infliximab package labeling each contains a warning regarding the risk of tuberculosis infection and cautioning use in patients that have a history of tuberculosis or are predisposed to infection. Adalimumab and infliximab both have a black box warning, while etanercept has a bolded warning relaying the risk of tuberculosis. Moreover, certain malignancies, such as lymphoma, have been observed with use of these agents, but a direct causal relationship has not yet been established. Per FDA recommendation, larger, long-term patient registries may provide data for additional monitoring for anti-TNF-associated lymphoma.

Adalimumab, administered biweekly as per the manufacturer's product labeling, is priced comparatively with other available biologic agents. However, the potential remains for the use of adalimumab in the absence of methotrexate at a once-weekly dosing schedule, which would almost double the cost of therapy compared with a standard regimen of a competing agent.

Since adalimumab currently offers no apparent clinical or financial advantages over its competitors, selection of biologic DMARD agents will thus depend on individual patient presentation and the clinical judgment of providers.

Recommendations

As with the other biological agents used in the treatment of rheumatoid arthritis, it is recommended that ADALIMUMAB remain a non-formulary agent at both national and VISN levels and be added to the **Criteria for use for Leflunomide, Etanercept, and Infliximab in the Treatment of Rheumatoid Arthritis,** located at **(http://vaww.pbm.med.va.gov/criteria/lef_etan_infcriteria.pdf).**

References:

1. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 update. Arthritis Rheum 2002; 46(2): 328-46.

2. Humira® (adalimumab) [package insert]. North Chicago, IL: Abbott Laboratories; December 2002.

3. Fox DA. Cytokine blockade as a new strategy to treat rheumatoid arthritis: Inhibition of tumor necrosis factor. Arch Intern Med 2000; 160 (4): 437-444.

4. Choy EHS, Panayi GS. Mechanisms of disease: Cytokine pathways and joint inflammation in rheumatoid arthritis. N Engl J Med 2001; 344(12): 907-16.

5. Bingham CO. The pathogenesis of rheumatoid arthritis: Pivotal cytokines in bone degradation and inflammation. J Rheumatol 2002; 26 (suppl 65): 3-9.

6. Dayer JM. Interleukin 1 or tumor necrosis factor-α: Which is the real target in rheumatoid arthritis? J Rheumatol 2002; 26 (suppl 65): 10-15.

7. Seymour HE, Worsley A, Smith JM, et al. Anti TNF agents for rheumatoid arthritis. Br J Clin Pharmacol 2001; 51(3): 201-8.

8. Pisetsky DS. Tumor necrosis factor blockers in rheumatoid arthritis. N Engl J Med 2000. 342(11): 810-811.

9. Schuna AA, Megeff C. New drugs for the treatment of rheumatoid arthritis. Am J Health Syst Pharm 2000; 57(3): 225-34.

10. Kempeni J. Update on D2E7: A fully human anti-tumor necrosis factor-α monoclonal antibody. Ann Rheum Dis 2000; 59 (suppl 1): i44-5.

11. Rau R. Adalimumab (a fully human anti-tumor necrosis factor-α monoclonal antibody) in the treatment of active rheumatoid arthritis: The initial results of five trials. Ann Rheum Dis 2002; 61(suppl II): ii70-3.

12. Kempeni J. Preliminary results of early clinical trials with fully human anti-TNF-α monoclonal antibody D2E7. Ann Rheum Dis 1999; 58(suppl 1): I70-2.

13. den Broeder A, van de Putte LB, Rau R, et al. A single-dose placebo controlled study of the fully human anti-tumor necrosis factor-α antibody adalimumab (D2E7) in patients with rheumatoid arthritis. J Rheumatology 2002; 29(11): 2288-98.

14. Salfeld J, Kaymakcalan Z, Tracey D, et al. Generation of fully human anti-TNF antibody D2E7 (abstract 147). Arthritis Rheum 1998; 41(9): s57.

15. Schiff M, Furst DE, Strand V, et al. A randomized, controlled, safety trial of adalimumab (D2E7), a fully human anti-TNF monoclonal antibody, given to RA patients in combination with standard rheumatologic care: The STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis) Trial. Abstract presented at: The European Congress of Rheumatology, June 14, 2002, Stockholm, Sweden.

16. Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995; 38:727-735.

17. Sharp JT, Lidsky MD, Collins LC, et al. Methods of scoring the progression of radiologic changes on rheumatoid arthritis: Correlation of radiologic, clinical, and laboratory abnormalities. Arthritis Rheum 1971; 14: 706-20.

18. Sharp JT, Young DY, Bluhm GB, et al. How many joints in the hands and wrists should be included in a score of radiologic abnormalities used to assess rheumatoid arthritis? Arthritis Rheum 1985; 28:1326-35.

19. Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti-tumor necrosis factor-α monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate. The ARMADA Trial. Arthritis & Rheum 2003; 48(1): 35-45.

20. Kavanaugh AF, Weinblatt M, Keystone E, et al. The ARMADA Trial: 12-month efficacy and safety of combination therapy with adalimumab (D2E7), the first fully human anti-TNF monoclonal antibody, and methotrexate (MTX) in patients with active rheumatoid arthritis. Abstract presented at: The European Congress of Rheumatology, June 12-15, 2002, Stockholm, Sweden.

21. van de Putte LB Atkins C, Malaise M, et al. Efficacy and safety of adalimumab (D2E7), the first fully human anti-TNF monoclonal antibody, in patients with rheumatoid arthritis who failed previous DMARD therapy: 6-month results from a phase III study. Abstract presented at: The European Congress of Rheumatology, June 12-15, 2002, Stockholm, Sweden.

22. Keystone E, Kavanaugh AF, Sharp J, et al. Adalimumab (D2E7), a fully human anti-TNF-α monoclonal antibody, inhibits the progression of structural joint damage in patients with active RA despite concomitant methotrexate therapy. Abstract presented at: The 66th Annual Meeting of the American College of Rheumatology, October 24-29, 2002, New Orleans, LA.

23. Furst DE, Fleischmann R, Birbara C, et al. Efficacy of adalimumab (D2E7), a fully human anti-TNF monoclonal antibody, administered to rheumatoid arthritis patients in combination with other antirheumatic therapy in the STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis) Trial. Abstract presented at: The European Congress of Rheumatology, June 12-15, 2002, Stockholm, Sweden.

24. Burmester GR, van de Putte LB, Rau R, et al. 2-Year experience with adalimumab (D2E7), the first fully human anti-TNF monoclonal antibody, in patients with DMARD-refractory rheumatoid arthritis. Abstract presented at: The European Congress of Rheumatology, June 12-15, 2002, Stockholm, Sweden.

25. Gomez-Reino JJ, Carmona L, Valverde VR, et al. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: A multicenter active-surveillance report. Arthritis Rheum 2003; 48(8): 2122-27.

26. Bresnihan B Cunnane G. Infection complications associated with the use of biologic agents. Rheum Dis Clin N Am 2003; (29): 185-202.

27. Enbrel® (etanercept) [package insert]. Seattle, WA: Immunex Corp; October 2002.

28. Remicade® (infliximab) [package insert]. Malvern, PA: Centocor, Inc.; June 2002.

29. Anakinra® (kineret) [package insert]. Thousand Oaks, CA: Amgen; October 2002.

30. FDA Advisory Committee. Arthritis committee will discuss risk of lymphoma with TNF inhibitors at March 4 meeting. Available at www.fdaadvisorycommittee.com. Accessed 09/2003.

31. FDA Advisory Committee. TNF inhibitor labeling on risk of lymphoma should caution against comparisons between agents. Available at www.fdaadvisorycommittee.com. Accessed 09/2003.

Prepared by: Marie Sales, Pharm.D., Research Associate/Clinical Pharmacy Specialist
Department of Veterans Affairs Pharmacy Benefits Management/Strategic Healthcare Group
Date: September 2003