CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

sBLA 125057/110

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use HUMIRA safely and effectively. See full prescribing information for HUMIRA.

HUMIRA (adalimumab) Injection, Solution for Subcutaneous use
Initial U.S. Approval: 2002

WARNING: RISK OF SERIOUS INFECTIONS
See full prescribing information for complete boxed warning.
Tuberculosis (TB), invasive fungal, and other opportunistic infections, some fatal, have occurred in patients treated with HUMIRA. Perform test for latent TB; if positive, start treatment for TB prior to starting HUMIRA. Monitor all patients for active TB during treatment, even if initial latent TB test is negative (5.1)

RECENT MAJOR CHANGES

Indications and Usage, Crohn's Disease (1.4)	2/2007
Indications and Usage, Plaque Psoriasis (1.5)	1/2008
Dosage and Administration, Crohn's Disease (2.2)	7/2007
Dosage and Administration, Plaque Psoriasis (2.3)	1/2008
Warnings and Precautions, Serious Infections (5.1)	2/2007
Warnings and Precautions, Malignancies (5.2)	1/2008
Warnings and Precautions, Immunizations (5.10)	2/2007

INDICATIONS AND USAGE

HUMIRA is a tumor necrosis factor (TNF) blocker indicated for treatment of:

Rheumatoid Arthritis (RA) (1.1)

- Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active disease.

Psoriatic Arthritis (1.2)

- Reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function.

Ankylosing Spondylitis (1.3)

- Reducing signs and symptoms in patients with active disease.

Crohn's Disease (1.4)

- Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Plaque Psoriasis (1.5)

- 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.

DOSAGE AND ADMINISTRATION

HUMIRA is administered by subcutaneous injection.

Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis (2.1)

- 40 mg every other week. Some patients with RA not receiving methotrexate may benefit from increasing the frequency to 40 mg every week.

Crohn's Disease (2.2)

- Initial dose (Day 1) is 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose of 40 mg every other week.

Plaque Psoriasis (2.3)

- 80 mg initial dose, followed by 40 mg every other week starting one week after initial dose.

DOSAGE FORMS AND STRENGTHS

- 40 mg/0.8 mL in a single-use prefilled pen (HUMIRA Pen) (3)
- 40 mg/0.8 mL in a single-use prefilled glass syringe (3)

CONTRAINDICATIONS

- None (4)

WARNINGS AND PRECAUTIONS

- Serious infections – do not start HUMIRA during an active infection. If an infection develops, monitor carefully, and stop HUMIRA if infection becomes serious (5.1)
- Malignancies – are seen more often than in controls, and lymphoma is seen more often than in the general population (5.2)
- Anaphylaxis or serious allergic reactions may occur (5.3)
- Hepatitis B virus reactivation – monitor HBV carriers during and several months after therapy. If reactivation occurs, stop HUMIRA and begin anti-viral therapy (5.4)
- Demyelinating disease, exacerbation or new onset, may occur (5.5)
- Cytopenias, pancytopenia – advise patients to seek immediate medical attention if symptoms develop, and consider stopping HUMIRA (5.6)
- Heart failure, worsening or new onset, may occur (5.8)
- Lupus-like syndrome – stop HUMIRA if syndrome develops (5.9)

ADVERSE REACTIONS

Most common adverse reactions (incidence >10%): infections (e.g. upper respiratory, sinusitis), injection site reactions, headache and rash (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Abbott Laboratories at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Anakinra – increased risk of serious infection (5.7, 7.1)
- Live vaccines – should not be given with HUMIRA (5.10, 7.2)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Physicians are encouraged to enroll pregnant patients in the HUMIRA pregnancy registry by calling 1-877-311-8972 (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised Jan 2008

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS INFECTIONS

Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation), invasive fungal infections, and other opportunistic infections, have been observed in patients receiving HUMIRA. Some of these infections have been fatal. Anti-tuberculosis treatment of patients with latent tuberculosis infection reduces the risk of reactivation in patients receiving treatment with HUMIRA. However, active tuberculosis has developed in patients receiving HUMIRA whose screening for latent tuberculosis infection was negative.

Patients should be evaluated for tuberculosis risk factors and be tested for latent tuberculosis infection prior to initiating HUMIRA and during therapy. Treatment of latent tuberculosis infection should be initiated prior to therapy with HUMIRA. Physicians should monitor patients receiving HUMIRA for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis infection.*[See Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis

HUMIRA is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. HUMIRA can be used alone or in combination with methotrexate or other disease-modifying anti-rheumatic drugs (DMARDs).

1.2 Psoriatic Arthritis

HUMIRA is indicated for reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis. HUMIRA can be used alone or in combination with DMARDs.

1.3 Ankylosing Spondylitis

HUMIRA is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

1.4 Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. HUMIRA is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

1.5 Plaque Psoriasis

HUMIRA is indicated 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 [*see Boxed WARNINGS and Warnings and Precautions (5)]*.

2 DOSAGE AND ADMINISTRATION

HUMIRA is administered by subcutaneous injection.

2.1 Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis

The recommended dose of HUMIRA for adult patients with rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis is 40 mg administered every other week. Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics or other DMARDs may be continued during treatment with HUMIRA. In rheumatoid arthritis, some patients not taking concomitant methotrexate may derive additional benefit from increasing the dosing frequency of HUMIRA to 40 mg every week.

2.2 Crohn's Disease

The recommended HUMIRA dose regimen for adult patients with Crohn's disease is 160 mg initially at Day 1 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose of 40 mg every other week. Aminosalicylates, corticosteroids, and/or immunomodulatory agents (e.g., 6-mercaptopurine and azathioprine) may be continued during treatment with HUMIRA. The use of HUMIRA in Crohn's disease beyond one year has not been evaluated in controlled clinical studies.

2.3 Plaque Psoriasis

The recommended dose of HUMIRA for adult patients with plaque psoriasis is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose. The use of HUMIRA in moderate to severe chronic plaque psoriasis beyond one year has not been evaluated in controlled clinical studies.

2.4 General Considerations for Administration

HUMIRA is intended for use under the guidance and supervision of a physician. A patient may self-inject HUMIRA if a physician determines that it is appropriate, and with medical follow-up, as necessary, after proper training in subcutaneous injection technique.

The solution in the HUMIRA Pen or prefilled syringe should be carefully inspected visually for particulate matter and discoloration prior to subcutaneous administration. If particulates and discolorations are noted, the product should not be used. HUMIRA does not contain preservatives; therefore, unused portions of drug remaining from the syringe should be discarded. NOTE: The needle cover of the syringe contains dry rubber (latex), which should not be handled by persons sensitive to this substance.

Patients using the HUMIRA Pen or prefilled syringe should be instructed to inject the full amount in the syringe (0.8 mL), which provides 40 mg of HUMIRA, according to the directions provided in the Medication Guide *[see Patient Counseling Information (17.3)]*.

Injection sites should be rotated and injections should never be given into areas where the skin is tender, bruised, red or hard.

3 DOSAGE FORMS AND STRENGTHS

- **Pen**

A single-use pen (HUMIRA Pen), containing a 1 mL prefilled glass syringe with a fixed 27 gauge ½ inch needle, providing 40 mg (0.8 mL) of HUMIRA.

- **Prefilled Syringe**

A single-use, 1 mL prefilled glass syringe with a fixed 27 gauge ½ inch needle, providing 40 mg (0.8 mL) of HUMIRA.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Serious infections, sepsis, tuberculosis and cases of opportunistic infections, including fatalities, have been reported with the use of TNF blocking agents including HUMIRA. Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their rheumatoid arthritis could predispose them to infections. In postmarketing experience, infections have been observed with various pathogens including viral, bacterial, fungal and protozoal organisms. Infections have been noted in all organ systems and have been reported in patients receiving HUMIRA alone or in combination with immunosuppressive agents.

Treatment with HUMIRA should not be initiated in patients with active infections including chronic or localized infections. Patients who develop a new infection while undergoing treatment with HUMIRA should be monitored closely. Administration of HUMIRA should be discontinued if a patient develops a serious infection. Physicians should exercise caution when considering the use of HUMIRA in patients with a history of recurrent infection or underlying conditions which may predispose them to infections, or patients who have resided in regions where tuberculosis and histoplasmosis are endemic. The benefits and risks of HUMIRA treatment should be carefully considered before initiation of HUMIRA therapy.

As observed with other TNF blocking agents, tuberculosis associated with the administration of HUMIRA in clinical trials has been reported. While cases were observed at all doses, the incidence of tuberculosis reactivations was particularly increased at doses of HUMIRA that were higher than the recommended dose.

Before initiation of therapy with HUMIRA, patients should be evaluated for tuberculosis risk factors and should be tested for latent tuberculosis infection. Treatment of latent tuberculosis infections should be initiated prior to therapy with HUMIRA. When tuberculin skin testing is performed for latent tuberculosis infection, an induration size of 5 mm or greater should be considered positive, even if vaccinated previously with Bacille Calmette-Guerin (BCG). If latent infection is diagnosed, appropriate prophylaxis should be instituted in accordance with the current guidelines from the Centers for Disease Control and Prevention.

The possibility of undetected latent tuberculosis should be considered, especially in patients who have immigrated from or traveled to countries with a high prevalence of tuberculosis or had close contact with a person with active tuberculosis. All patients treated with HUMIRA should have a thorough history taken prior to initiating therapy. Some patients who have previously received treatment for latent or active tuberculosis have developed active tuberculosis while being treated with TNF blocking agents. Anti-tuberculosis therapy should be considered prior to initiation of HUMIRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Anti-tuberculosis therapy prior to initiating HUMIRA should also be considered in patients who have several, or highly significant, risk factors for tuberculosis infection and have a negative test for latent tuberculosis, but the decision to initiate anti-tuberculosis therapy in these patients should only be made after taking into account both the risk for latent tuberculosis infection and the risks of anti-tuberculosis therapy. If necessary, consultation should occur with a physician with expertise in the treatment of tuberculosis.

Patients receiving HUMIRA should be monitored for signs and symptoms of active tuberculosis, particularly because tests for latent tuberculosis infection may be falsely negative. Patients should be instructed to seek medical advice if signs or symptoms (e.g., persistent cough, wasting, weight loss, low grade fever) suggestive of a tuberculosis infection occur.

5.2 Malignancies

In the controlled portions of clinical trials of some TNF-blocking agents, including HUMIRA, more cases of malignancies have been observed among patients receiving those TNF blockers compared to control patients. During the controlled portions of HUMIRA trials in patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and plaque psoriasis, malignancies, other than lymphoma and non-melanoma (basal cell and squamous cell) skin cancer, were observed at a rate (95% confidence interval) of 0.6 (0.3, 1.0)/100 patient-years among 3853 HUMIRA-treated patients versus a rate of 0.4 (0.2,

1.0)/100 patient-years among 2183 control patients (median duration of treatment of 5.5 months for HUMIRA-treated patients and 3.9 months for control-treated patients). The size of the control group and limited duration of the controlled portions of studies precludes the ability to draw firm conclusions. In the controlled and uncontrolled open-label portions of the clinical trials of HUMIRA, the more frequently observed malignancies, other than lymphoma and non-melanoma skin cancer, were breast, colon, prostate, lung, and melanoma. These malignancies in HUMIRA-treated and control-treated patients were similar in type and number to what would be expected in the general population.[1] During the controlled portions of HUMIRA rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and plaque psoriasis trials, the rate (95% confidence interval) of non-melanoma (basal cell and squamous cell) skin cancers was 0.9 (0.57, 1.35)/100 patient-years among HUMIRA-treated patients and 0.3 (0.08, 0.80)/100 patient-years among control patients. The potential role of TNF blocking therapy in the development of malignancies is not known.

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. In controlled trials in patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and plaque psoriasis, 2 lymphomas were observed among 3853 HUMIRA-treated patients versus 1 among 2183 control patients. In combining the controlled and uncontrolled open-label portions of these clinical trials with a median duration of approximately 2 years, including 6539 patients and over 16,000 patient-years of therapy, the observed rate of lymphomas is approximately 0.11/100 patient-years. This is approximately 3-fold higher than expected in the general population.[1] Rates in clinical trials for HUMIRA cannot be compared to rates of clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. Patients with rheumatoid arthritis, particularly those with highly active disease, are at a higher risk for the development of lymphoma.

5.3 Hypersensitivity Reactions

In postmarketing experience, anaphylaxis and angioneurotic edema have been reported rarely following HUMIRA administration. If an anaphylactic or other serious allergic reaction occurs, administration of HUMIRA should be discontinued immediately and appropriate therapy instituted. In clinical trials of HUMIRA, allergic reactions overall (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed in approximately 1% of patients.

5.4 Hepatitis B Virus Reactivation

Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF blocker therapy. Prescribers should exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with TNF blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, HUMIRA should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. Therefore, prescribers should exercise caution when considering resumption of HUMIRA therapy in this situation and monitor patients closely.

5.5 Neurologic Reactions

Use of TNF blocking agents, including HUMIRA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease. Prescribers should exercise caution in considering the use of HUMIRA in patients with preexisting or recent-onset central nervous system demyelinating disorders.

5.6 Hematological Reactions

Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., thrombocytopenia, leukopenia) have been infrequently reported with HUMIRA *[see Adverse Reactions (6)]*. The causal relationship of these reports to HUMIRA remains unclear. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on HUMIRA. Discontinuation of HUMIRA therapy should be considered in patients with confirmed significant hematologic abnormalities.

5.7 Use with Anakinra

Serious infections were seen in clinical studies with concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocking agent, with no added benefit. Because of the nature of the adverse reactions seen with this combination therapy, similar toxicities may also result from combination of anakinra and other TNF blocking agents. Therefore, the combination of HUMIRA and anakinra is not recommended *[see Drug Interactions (7.1)]*.

5.8 Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. Cases of worsening CHF have also been observed with HUMIRA. HUMIRA has not been formally studied in patients with CHF; however, in clinical trials of another TNF blocker, a higher rate of serious CHF-related adverse reactions was observed. Physicians should exercise caution when using HUMIRA in patients who have heart failure and monitor them carefully.

5.9 Autoimmunity

Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with HUMIRA, treatment should be discontinued *[see Adverse Reactions (6.1)]*.

5.10 Immunizations

In a placebo-controlled clinical trial of patients with rheumatoid arthritis, no difference was detected in anti-pneumococcal antibody response between HUMIRA and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with HUMIRA. Similar proportions of patients developed protective levels of anti-influenza antibodies between HUMIRA and placebo treatment groups; however, titers in aggregate to influenza antigens were moderately lower in patients receiving HUMIRA. The clinical significance of this is unknown. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving HUMIRA.

5.11 Immunosuppression

The possibility exists for TNF blocking agents, including HUMIRA, to affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 64 patients with rheumatoid arthritis treated with HUMIRA, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector T- and B-cells and NK-cells, monocyte/macrophages, and neutrophils. The impact of treatment with HUMIRA on the development and course of malignancies, as well as active and/or chronic infections, is not fully

understood *[see Warnings and Precautions (5.1, 5.2) and Adverse Reactions (6.1)]*. The safety and efficacy of HUMIRA in patients with immunosuppression have not been evaluated.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

The most serious adverse reactions were *[see Warnings and Precautions (5)]*:

- Serious Infections
- Neurologic Reactions
- Malignancies

The most common adverse reaction with HUMIRA was injection site reactions. In placebo-controlled trials, 20% of patients treated with HUMIRA developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 14% of patients receiving placebo. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

The proportion of patients who discontinued treatment due to adverse reactions during the double-blind, placebo-controlled portion of Studies RA-I, RA-II, RA-III and RA-IV was 7% for patients taking HUMIRA and 4% for placebo-treated patients. The most common adverse reactions leading to discontinuation of HUMIRA were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%).

Because clinical trials are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not predict the rates observed in a broader patient population in clinical practice.

Infections

In placebo-controlled rheumatoid arthritis trials, the rate of infection was 1 per patient-year in the HUMIRA-treated patients and 0.9 per patient-year in the placebo-treated patients. The infections consisted primarily of upper respiratory tract infections, bronchitis and urinary tract infections. Most patients continued on HUMIRA after the infection resolved. The incidence of serious infections was 0.04 per patient-year in HUMIRA treated patients and 0.02 per patient-year in placebo-treated patients. Serious infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis *[see Warnings and Precautions (5.1)]*.

Tuberculosis and Opportunistic Infections

In completed and ongoing global clinical studies that include over 13,000 patients, the overall rate of tuberculosis is approximately 0.26 per 100 patient-years. In over 4500 patients in the US and Canada, the rate is approximately 0.07 per 100 patient-years. These studies include reports of miliary, lymphatic, peritoneal, as well as pulmonary. Most of the cases of tuberculosis occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease. Cases of opportunistic infections have also been reported in these clinical trials at an overall rate of approximately 0.075/100 patient-years. Some cases of opportunistic infections and tuberculosis have been fatal *[see Warnings and Precautions (5.1)]*.

Malignancies

More cases of malignancy have been observed in HUMIRA-treated patients compared to control-treated patients in clinical trials *[see Warnings and Precautions (5.2)]*.

Autoantibodies

In the rheumatoid arthritis controlled trials, 12% of patients treated with HUMIRA and 7% of placebo-treated patients that had negative baseline ANA titers developed positive titers at week 24. Two patients out of 3046 treated with HUMIRA developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with HUMIRA on the development of autoimmune diseases is unknown.

Immunogenicity

Patients in Studies RA-I, RA-II, and RA-III were tested at multiple time points for antibodies to adalimumab during the 6- to 12-month period. Approximately 5% (58 of 1062) of adult rheumatoid arthritis patients receiving HUMIRA developed low-titer antibodies to adalimumab at least once during treatment, which were neutralizing *in vitro*. Patients treated with concomitant methotrexate had a lower rate of antibody development than patients on HUMIRA monotherapy (1% versus 12%). No apparent correlation of antibody development to adverse reactions was observed. With monotherapy, patients receiving every other week dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the recommended dosage of 40 mg every other week as monotherapy, the ACR 20 response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of HUMIRA is unknown.

In patients with ankylosing spondylitis, the rate of development of antibodies to adalimumab in HUMIRA-treated patients was comparable to patients with rheumatoid arthritis. In patients with psoriatic arthritis, the rate of antibody development in patients receiving HUMIRA monotherapy was comparable to patients with rheumatoid arthritis; however, in patients receiving concomitant methotrexate the rate was 7% compared to 1% in rheumatoid arthritis. In patients with Crohn's disease, the rate of antibody development was 2.6%. The immunogenicity rate was 8% for plaque psoriasis patients who were treated with HUMIRA monotherapy.

The data reflect the percentage of patients whose test results were considered positive for antibodies to adalimumab in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to adalimumab with the incidence of antibodies to other products may be misleading.

Other Adverse Reactions

The data described below reflect exposure to HUMIRA in 2468 patients, including 2073 exposed for 6 months, 1497 exposed for greater than one year and 1380 in adequate and well-controlled studies (Studies RA-I, RA-II, RA-III, and RA-IV). HUMIRA was studied primarily in placebo-controlled trials and in long-term follow up studies for up to 36 months duration. The population had a mean age of 54 years, 77% were female, 91% were Caucasian and had moderately to severely active rheumatoid arthritis. Most patients received 40 mg HUMIRA every other week.

Table 1 summarizes reactions reported at a rate of at least 5% in patients treated with HUMIRA 40 mg every other week compared to placebo and with an incidence higher than placebo. Adverse reaction rates in patients treated with HUMIRA 40 mg weekly were similar to rates in patients treated with HUMIRA 40 mg every other week. In Study RA-III, the types and frequencies of adverse reactions in the second year open-label extension were similar to those observed in the one-year double-blind portion.

Table 1: Adverse Reactions Reported by ≥5% of Patients Treated with HUMIRA During Placebo-Controlled Period of Rheumatoid Arthritis Studies

	HUMIRA 40 mg subcutaneous Every Other Week	Placebo
	(N=705)	(N=690)
Adverse Reaction (Preferred Term)	Percentage	Percentage
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

* Laboratory test abnormalities were reported as adverse reactions in European trials

** Does not include erythema and/or itching, hemorrhage, pain or swelling

Other Adverse Reactions

Other infrequent serious adverse reactions occurring at an incidence of less than 5% in rheumatoid arthritis patients treated with HUMIRA were:

Body As A Whole: Fever, infection, pain in extremity, pelvic pain, sepsis, surgery, thorax pain, tuberculosis reactivated

Cardiovascular System: Arrhythmia, atrial fibrillation, cardiovascular disorder, chest pain, congestive heart failure, coronary artery disorder, heart arrest, hypertensive encephalopathy, myocardial infarct, palpitation, pericardial effusion, pericarditis, syncope, tachycardia, vascular disorder

Collagen Disorder: Lupus erythematosus syndrome

Digestive System: Cholecystitis, cholelithiasis, esophagitis, gastroenteritis, gastrointestinal disorder, gastrointestinal hemorrhage, hepatic necrosis, vomiting

Endocrine System: Parathyroid disorder

Hemic And Lymphatic System: Agranulocytosis, granulocytopenia, leukopenia, lymphoma like reaction, pancytopenia, polycythemia *[see Warnings and Precautions (5.6)]*

Metabolic And Nutritional Disorders: Dehydration, healing abnormal, ketosis, paraproteinemia, peripheral edema

Musculo-Skeletal System: Arthritis, bone disorder, bone fracture (not spontaneous), bone necrosis, joint disorder, muscle cramps, myasthenia, pyogenic arthritis, synovitis, tendon disorder

Neoplasia: Adenoma, carcinomas such as breast, gastrointestinal, skin, urogenital, and others; lymphoma and melanoma

Nervous System: Confusion, multiple sclerosis, paresthesia, subdural hematoma, tremor

Respiratory System: Asthma, bronchospasm, dyspnea, lung disorder, lung function decreased, pleural effusion, pneumonia

Skin And Appendages: Cellulitis, erysipelas, herpes zoster

Special Senses: Cataract

Thrombosis: Thrombosis leg

Urogenital System: Cystitis, kidney calculus, menstrual disorder, pyelonephritis

Psoriatic Arthritis and Ankylosing Spondylitis Clinical Studies

HUMIRA has been studied in 395 patients with psoriatic arthritis in two placebo-controlled trials and in an open label study and in 393 patients with ankylosing spondylitis in two placebo-controlled studies. The safety profile for patients with psoriatic arthritis and ankylosing spondylitis treated with HUMIRA 40 mg every other week was similar to the safety profile seen in patients with rheumatoid arthritis, HUMIRA Studies RA-I through IV. In the clinical trials of patients with psoriatic arthritis and ankylosing spondylitis, elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving HUMIRA than in controls, both when HUMIRA was given as monotherapy and when it was used in combination with other immunosuppressive agents. Most elevations of ALT and AST observed were in the range of 1.5 to 3 times the upper limit of normal. In general, patients who developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of HUMIRA, or modification of concomitant medications.

Crohn's Disease Clinical Studies

HUMIRA has been studied in 1478 patients with Crohn's disease in four placebo-controlled and two open-label extension studies. The safety profile for patients with Crohn's disease treated with HUMIRA was similar to the safety profile seen in patients with rheumatoid arthritis.

Plaque Psoriasis Clinical Studies

HUMIRA has been studied in 1696 patients with plaque psoriasis in placebo-controlled and open-label extension studies. The safety profile for patients with plaque psoriasis treated with HUMIRA was similar to the safety profile seen in patients with rheumatoid arthritis with the following exceptions. In the placebo-controlled portions of the clinical trials in plaque psoriasis patients, HUMIRA-treated patients had a higher incidence of arthralgia when compared to controls (3% vs. 1%).

Elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving HUMIRA than in controls. Most elevations of ALT and AST observed were in the range of 1.5 to 3 times the upper limit of normal. In general, patients who developed ALT and AST elevations were asymptomatic, and most of the abnormalities decreased or resolved with either continuation or discontinuation of HUMIRA.

6.2 Postmarketing Experience

Adverse reactions have been reported during post-approval use of HUMIRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to HUMIRA exposure.

Hematologic reactions: Thrombocytopenia *[see Warnings and Precautions (5.6)]*

Hypersensitivity reactions: Anaphylaxis, angioneurotic edema *[see Warnings and Precautions (5.3)]*

Respiratory disorders: Interstitial lung disease, including pulmonary fibrosis

Skin reactions: Cutaneous vasculitis, erythema multiforme

7 DRUG INTERACTIONS

7.1 Anakinra

Concurrent administration of anakinra (an interleukin-1 antagonist) and another TNF-blocking agent has been associated with an increased risk of serious infections, an increased risk of neutropenia and no additional benefit compared to these medicinal products alone. Therefore, the combination of anakinra with other TNF-blocking agents, including HUMIRA, may also result in similar toxicities *[see Warnings and Precautions (5.7)]*.

7.2 Live Vaccines

Live vaccines should not be given concurrently with HUMIRA *[see Warnings and Precautions (5.10)]*.

7.3 Methotrexate

HUMIRA has been studied in rheumatoid arthritis patients taking concomitant methotrexate. Although methotrexate reduced the apparent adalimumab clearance *[see Clinical Pharmacology (12.3)]*, the data do not suggest the need for dose adjustment of either HUMIRA or methotrexate.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B - An embryo-fetal perinatal developmental toxicity study has been performed in cynomolgus monkeys at dosages up to 100 mg/kg (266 times human AUC when given 40 mg subcutaneously with methotrexate every week or 373 times human AUC when given 40 mg subcutaneously without methotrexate) and has revealed no evidence of harm to the fetuses due to adalimumab. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction and developmental studies are not always predictive of human response, HUMIRA should be used during pregnancy only if clearly needed.

Pregnancy Registry: To monitor outcomes of pregnant women exposed to HUMIRA, a pregnancy registry has been established. Physicians are encouraged to register patients by calling 1-877-311-8972.

8.3 Nursing Mothers

It is not known whether adalimumab is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from HUMIRA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of HUMIRA in pediatric patients have not been established.

8.5 Geriatric Use

A total of 519 rheumatoid arthritis patients 65 years of age and older, including 107 patients 75 years and older, received HUMIRA in clinical studies RA-I through IV. No overall difference in effectiveness was observed between these subjects and younger subjects. The frequency of serious infection and malignancy among HUMIRA treated subjects over age 65 was higher than for those under age 65. Because there is a higher incidence of infections and malignancies in the elderly population in general, caution should be used when treating the elderly.

10 OVERDOSAGE

Doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

11 DESCRIPTION

HUMIRA (adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF). HUMIRA was created using phage display technology resulting in an antibody with human derived heavy and light chain variable regions and human IgG1:k constant regions. Adalimumab is produced by recombinant DNA technology in a mammalian cell expression system and is purified by a process that includes specific viral inactivation and removal steps. It consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons.

HUMIRA is supplied as a sterile, preservative-free solution of adalimumab for subcutaneous administration. The drug product is supplied as either a single-use, prefilled pen (HUMIRA Pen) or as a single-use, 1 mL prefilled glass syringe. Enclosed within the pen is a single-use, 1 mL prefilled glass syringe. The solution of HUMIRA is clear and colorless, with a pH of about 5.2. Each syringe delivers 0.8 mL (40 mg) of drug product. Each 0.8 mL of HUMIRA contains 40 mg adalimumab, 4.93 mg sodium chloride, 0.69 mg monobasic sodium phosphate dihydrate, 1.22 mg dibasic sodium phosphate dihydrate, 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. Sodium hydroxide added as necessary to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Adalimumab binds specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also lyses surface TNF expressing cells *in vitro* in the presence of complement. Adalimumab does not bind or inactivate lymphotoxin (TNF-beta). TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis patients and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. Increased levels of TNF are also found in psoriasis (Ps) plaques. In plaque psoriasis, treatment with HUMIRA may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamic activities and the mechanism(s) by which HUMIRA exerts its clinical effects is unknown.

Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC_{50} of 1-2 X 10^{-10}M).

12.2 Pharmacodynamics

After treatment with HUMIRA, a decrease in levels of acute phase reactants of inflammation (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and serum cytokines (IL-6) was observed compared to baseline in patients with rheumatoid arthritis. A decrease in CRP levels was also observed in patients with Crohn's disease. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodeling responsible for cartilage destruction were also decreased after HUMIRA administration.

12.3 Pharmacokinetics

The maximum serum concentration (C_{max}) and the time to reach the maximum concentration (T_{max}) were 4.7 ± 1.6 µg/mL and 131 ± 56 hours respectively, following a single 40 mg subcutaneous administration of HUMIRA to healthy adult subjects. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64%. The pharmacokinetics of adalimumab were linear over the dose range of 0.5 to 10.0 mg/kg following a single intravenous dose.

The single dose pharmacokinetics of adalimumab in rheumatoid arthritis (RA) patients were determined in several studies with intravenous doses ranging from 0.25 to 10 mg/kg. The distribution volume (V_{ss}) ranged from 4.7 to 6.0 L. The systemic clearance of adalimumab is approximately 12 mL/hr. The mean terminal half-life was approximately 2 weeks, ranging from 10 to 20 days across studies. Adalimumab concentrations in the synovial fluid from five rheumatoid arthritis patients ranged from 31 to 96% of those in serum.

In RA patients receiving 40 mg HUMIRA every other week, adalimumab mean steady-state trough concentrations of approximately 5 µg/mL and 8 to 9 µg/mL, were observed without and with methotrexate (MTX), respectively. MTX reduced adalimumab apparent clearance after single and multiple dosing by 29% and 44% respectively, in patients with RA. Mean serum adalimumab trough levels at steady state increased approximately proportionally with dose following 20, 40, and 80 mg every other week and every week subcutaneous dosing. In long-term studies with dosing more than two years, there was no evidence of changes in clearance over time.

Adalimumab mean steady-state trough concentrations were slightly higher in psoriatic arthritis patients treated with 40 mg HUMIRA every other week (6 to 10 µg/mL and 8.5 to 12 µg/mL, without and with MTX, respectively) compared to the concentrations in RA patients treated with the same dose.

The pharmacokinetics of adalimumab in patients with ankylosing spondylitis were similar to those in patients with RA.

In patients with Crohn's disease, the loading dose of 160 mg HUMIRA on Week 0 followed by 80 mg HUMIRA on Week 2 achieves mean serum adalimumab trough levels of approximately 12 µg/mL at Week 2 and Week 4. Mean steady-state trough levels of approximately 7 µg/mL were observed at Week 24 and Week 56 in Crohn's disease patients after receiving a maintenance dose of 40 mg HUMIRA every other week.

In patients with plaque psoriasis, the mean steady-state trough concentration was approximately 5 to 6 µg/mL during adalimumab 40 mg every other week monotherapy treatment.

Population pharmacokinetic analyses in patients with RA revealed that there was a trend toward higher apparent clearance of adalimumab in the presence of anti-adalimumab antibodies, and lower clearance with increasing age in patients aged 40 to >75 years.

Minor increases in apparent clearance were also predicted in RA patients receiving doses lower than the recommended dose and in RA patients with high rheumatoid factor or CRP concentrations. These increases are not likely to be clinically important.

No gender-related pharmacokinetic differences were observed after correction for a patient's body weight. Healthy volunteers and patients with rheumatoid arthritis displayed similar adalimumab pharmacokinetics.

No pharmacokinetic data are available in patients with hepatic or renal impairment.

HUMIRA has not been studied in children.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES

14.1 Rheumatoid Arthritis

The efficacy and safety of HUMIRA were assessed in five randomized, double-blind studies in patients ≥ age 18 with active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR) criteria. Patients had at least 6 swollen and 9 tender joints. HUMIRA was administered subcutaneously in combination with methotrexate (MTX) (12.5 to 25 mg, Studies RA-I, RA-III and RA-V) or as monotherapy (Studies RA-II and RA-V) or with other disease-modifying anti-rheumatic drugs (DMARDs) (Study RA-IV).

Study RA-I evaluated 271 patients who had failed therapy with at least one but no more than four DMARDs and had inadequate response to MTX. Doses of 20, 40 or 80 mg of HUMIRA or placebo were given every other week for 24 weeks.

Study RA-II evaluated 544 patients who had failed therapy with at least one DMARD. Doses of placebo, 20 or 40 mg of HUMIRA were given as monotherapy every other week or weekly for 26 weeks.

Study RA-III evaluated 619 patients who had an inadequate response to MTX. Patients received placebo, 40 mg of HUMIRA every other week with placebo injections on alternate weeks, or 20 mg of HUMIRA weekly for up to 52 weeks. Study RA-III had an additional primary endpoint at 52 weeks of inhibition of disease progression (as detected by X-ray results). Upon completion of the first 52 weeks, 457 patients enrolled in an open-label extension phase in which 40 mg of HUMIRA was administered every other week for up to 5 years.

Study RA-IV assessed safety in 636 patients who were either DMARD-naive or were permitted to remain on their pre-existing rheumatologic therapy provided that therapy was stable for a minimum of 28 days. Patients were randomized to 40 mg of HUMIRA or placebo every other week for 24 weeks.

Study RA-V evaluated 799 patients with moderately to severely active rheumatoid arthritis of less than 3 years duration who were ≥18 years old and MTX naïve. Patients were randomized to receive either MTX (optimized to 20 mg/week by week 8), HUMIRA 40 mg every other week or HUMIRA/MTX combination therapy for 104 weeks. Patients were evaluated for signs and symptoms, and for radiographic progression of joint damage. The median disease duration among patients enrolled in the study was 5 months. The median MTX dose achieved was 20 mg.

Clinical Response

The percent of HUMIRA treated patients achieving ACR 20, 50 and 70 responses in Studies RA-II and III are shown in Table 2.

Table 2: ACR Responses in Studies RA-II and RA-III (Percent of Patients)

		Study RA-II Monotherapy (26 weeks)		**Study RA-III Methotrexate Combination (24 and 52 weeks)**	
Response	Placebo	HUMIRA 40 mg every other week	HUMIRA 40 mg weekly	Placebo/MTX	HUMIRA/MTX 40 mg every other week
	N=110	N=113	N=103	N=200	N=207
ACR20					
Month 6	19%	46%*	53%*	30%	63%*
Month 12	NA	NA	NA	24%	59%*
ACR50					
Month 6	8%	22%*	35%*	10%	39%*
Month 12	NA	NA	NA	10%	42%*
ACR70					
Month 6	2%	12%*	18%*	3%	21%*
Month 12	NA	NA	NA	5%	23%*

* $p<0.01$, HUMIRA vs. placebo

The results of Study RA-I were similar to Study RA-III; patients receiving HUMIRA 40 mg every other week in Study RA-I also achieved ACR 20, 50 and 70 response rates of 65%, 52% and 24%, respectively, compared to placebo responses of 13%, 7% and 3% respectively, at 6 months ($p<0.01$).

The results of the components of the ACR response criteria for Studies RA-II and RA-III are shown in Table 3. ACR response rates and improvement in all components of ACR response were maintained to week 104. Over the 2 years in Study RA-III, 20% of HUMIRA patients receiving 40 mg every other week (every other week) achieved a major clinical response, defined as maintenance of an ACR 70 response over a 6-month period.

ACR responses were maintained in similar proportions of patients for up to 5 years with continuous HUMIRA treatment in the open-label portion of Study RA-III.

Table 3: Components of ACR Response in Studies RA-II and RA-III

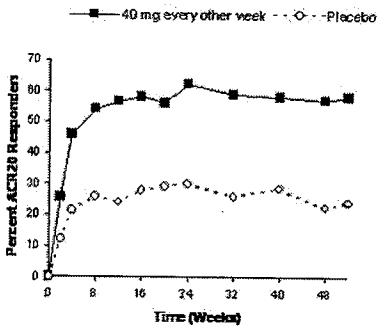
Parameter (median)	Study RA-II				Study RA-III			
	Placebo N=110		HUMIRA[a] N=113		Placebo/MTX N=200		HUMIRA[a]/MTX N=207	
	Baseline	Wk 26	Baseline	Wk 26	Baseline	Wk 24	Baseline	Wk 24
Number of tender joints (0-68)	35	26	31	16*	26	15	24	8*
Number of swollen joints (0-66)	19	16	18	10*	17	11	18	5*
Physician global assessment[b]	7.0	6.1	6.6	3.7*	6.3	3.5	6.5	2.0*
Patient global assessment[b]	7.5	6.3	7.5	4.5*	5.4	3.9	5.2	2.0*
Pain[b]	7.3	6.1	7.3	4.1*	6.0	3.8	5.8	2.1*
Disability index (HAQ)[c]	2.0	1.9	1.9	1.5*	1.5	1.3	1.5	0.8*
CRP (mg/dL)	3.9	4.3	4.6	1.8*	1.0	0.9	1.0	0.4*

a 40 mg HUMIRA administered every other week
b Visual analogue scale; 0 = best, 10 = worst
c Disability Index of the Health Assessment Questionnaire; 0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity
* $p<0.001$, HUMIRA vs. placebo, based on mean change from baseline

The time course of ACR 20 response for Study RA-III is shown in Figure 1.

In Study RA-III, 85% of patients with ACR 20 responses at week 24 maintained the response at 52 weeks. The time course of ACR 20 response for Study RA-I and Study RA-II were similar.

Figure 1: Study RA-III ACR 20 Responses over 52 Weeks



In Study RA-IV, 53% of patients treated with HUMIRA 40 mg every other week plus standard of care had an ACR 20 response at week 24 compared to 35% on placebo plus standard of care ($p<0.001$). No unique adverse reactions related to the combination of HUMIRA (adalimumab) and other DMARDs were observed.

In Study RA-V with MTX naïve patients with recent onset rheumatoid arthritis, the combination treatment with HUMIRA plus MTX led to greater percentages of patients achieving ACR responses than either MTX monotherapy or HUMIRA monotherapy at Week 52 and responses were sustained at Week 104 (see Table 4).

Table 4: ACR Response in Study RA-V (Percent of Patients)

Response	MTX[b] N=257	HUMIRA[c] N=274	HUMIRA/MTX N=268
ACR20			
Week 52	63%	54%	73%
Week 104	56%	49%	69%
ACR50			
Week 52	46%	41%	62%
Week 104	43%	37%	59%
ACR70			
Week 52	27%	26%	46%
Week 104	28%	28%	47%
Major Clinical Response[a]	28%	25%	49%

a Major clinical response is defined as achieving an ACR70 response for a continuous six month period
b $p<0.05$, HUMIRA/MTX vs. MTX for ACR 20
$p<0.001$, HUMIRA/MTX vs. MTX for ACR 50 and 70, and Major Clinical Response
c $p<0.001$, HUMIRA/MTX vs. HUMIRA

At Week 52, all individual components of the ACR response criteria for Study RA-V improved in the HUMIRA/MTX group and improvements were maintained to Week 104.

Radiographic Response

In Study RA-III, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and Joint Space Narrowing (JSN) score, at month 12 compared to baseline. At baseline, the median TSS was approximately 55 in the placebo and 40 mg every other week groups. The results are shown in Table 5. HUMIRA/MTX treated patients demonstrated less radiographic progression than patients receiving MTX alone at 52 weeks.

Table 5: Radiographic Mean Changes Over 12 Months in Study RA-III

	Placebo/MTX	HUMIRA/MTX 40 mg every other week	Placebo/MTX-HUMIRA/MTX (95% Confidence Interval*)	P-value**
Total Sharp score	2.7	0.1	2.6 (1.4, 3.8)	<0.001
Erosion score	1.6	0.0	1.6 (0.9, 2.2)	<0.001
JSN score	1.0	0.1	0.9 (0.3, 1.4)	0.002

*95% confidence intervals for the differences in change scores between MTX and HUMIRA.
**Based on rank analysis

In the open-label extension of Study RA-III, 77% of the original patients treated with any dose of HUMIRA were evaluated radiographically at 2 years. Patients maintained inhibition of structural damage, as measured by the TSS. Fifty-four percent had no progression of structural damage as defined by a change in the TSS of zero or less.

Fifty-five percent (55%) of patients originally treated with 40 mg HUMIRA every other week have been evaluated radiographically at 5 years. Patients had continued inhibition of structural damage with 50% showing no progression of structural damage defined by a change in the TSS of zero or less.

In Study RA-V, structural joint damage was assessed as in Study RA-III. Greater inhibition of radiographic progression, as assessed by changes in TSS, erosion score and JSN was observed in the HUMIRA/MTX combination group as compared to either the MTX or HUMIRA monotherapy group at Week 52 as well as at Week 104 (see Table 6).

Table 6: Radiographic Mean Change* in Study RA-V

		MTX[a] N=257	HUMIRA[a,b] N=274	HUMIRA/MTX N=268
52 Weeks	Total Sharp score	5.7 (4.2, 7.3)	3.0 (1.7, 4.3)	1.3 (0.5, 2.1)
	Erosion score	3.7 (2.7, 4.8)	1.7 (1.0, 2.4)	0.8 (0.4, 1.2)
	JSN score	2.0 (1.2, 2.8)	1.3 (0.5, 2.1)	0.5 (0.0, 1.0)
104 Weeks	Total Sharp score	10.4 (7.7, 13.2)	5.5 (3.6, 7.4)	1.9 (0.9, 2.9)
	Erosion score	6.4 (4.6, 8.2)	3.0 (2.0, 4.0)	1.0 (0.4, 1.6)
	JSN score	4.1 (2.7, 5.4)	2.6 (1.5, 3.7)	0.9 (0.3, 1.5)

* mean (95% confidence interval)
a $p<0.001$, HUMIRA/MTX vs. MTX at 52 and 104 weeks and for HUMIRA/MTX vs. HUMIRA at 104 weeks
b $p<0.01$, for HUMIRA/MTX vs. HUMIRA at 52 weeks

Physical Function Response

In studies RA-I through IV, HUMIRA showed significantly greater improvement than placebo in the disability index of Health Assessment Questionnaire (HAQ-DI) from baseline to the end of study, and significantly greater improvement than placebo in the health-outcomes as assessed by The Short Form Health Survey (SF 36). Improvement was seen in both the Physical Component Summary (PCS) and the Mental Component Summary (MCS).

In Study RA-III, the mean (95% CI) improvement in HAQ-DI from baseline at week 52 was 0.60 (0.55, 0.65) for the HUMIRA patients and 0.25 (0.17, 0.33) for placebo/MTX ($p<0.001$) patients. Sixty-three percent of HUMIRA-treated patients achieved a 0.5 or greater improvement in HAQ-DI at week 52 in the double-blind portion of the study. Eighty-two percent of these patients maintained that improvement through week 104 and a similar proportion of patients maintained this response through week 260 (5 years) of open label treatment. Mean improvement in the SF-36 was maintained through the end of measurement at week 156 (3 years).

In Study RA-V, the HAQ-DI and the physical component of the SF-36 showed greater improvement ($p<0.001$) for the HUMIRA/MTX combination therapy group versus either the MTX monotherapy or the HUMIRA monotherapy group at Week 52, which was maintained through Week 104.

14.2 Psoriatic Arthritis

The safety and efficacy of HUMIRA was assessed in two randomized, double-blind, placebo controlled studies in 413 patients with psoriatic arthritis. Upon completion of both studies, 383 patients enrolled in an open-label extension study, in which 40 mg HUMIRA was administered every other week.

Study PsA-I enrolled 313 adult patients with moderately to severely active psoriatic arthritis (>3 swollen and >3 tender joints) who had an inadequate response to NSAID therapy in one of the following forms: (1) distal interphalangeal (DIP) involvement (N=23); (2) polyarticular arthritis (absence of rheumatoid nodules and presence of plaque psoriasis) (N=210); (3) arthritis mutilans (N=1); (4) asymmetric psoriatic arthritis (N=77); or (5) ankylosing spondylitis-like (N=2). Patients on MTX therapy (158 of 313 patients) at enrollment (stable dose of ≤30 mg/week for >1 month) could continue MTX at the same dose. Doses of HUMIRA 40 mg or placebo every other week were administered during the 24-week double-blind period of the study.

Compared to placebo, treatment with HUMIRA resulted in improvements in the measures of disease activity (see Tables 7 and 8). Among patients with psoriatic arthritis who received HUMIRA, the clinical responses were apparent in some patients at the time of the first visit (two weeks) and were maintained up to 88 weeks in the ongoing open-label study. Similar responses were seen in patients with each of the subtypes of psoriatic arthritis, although few patients were enrolled with the arthritis mutilans and ankylosing spondylitis-like subtypes. Responses were similar in patients who were or were not receiving concomitant MTX therapy at baseline.

Patients with psoriatic involvement of at least three percent body surface area (BSA) were evaluated for Psoriatic Area and Severity Index (PASI) responses. At 24 weeks, the proportions of patients achieving a 75% or 90% improvement in the PASI were 59% and 42% respectively, in the HUMIRA group (N=69), compared to 1% and 0% respectively, in the placebo group (N=69) ($p<0.001$). PASI responses were apparent

in some patients at the time of the first visit (two weeks). Responses were similar in patients who were or were not receiving concomitant MTX therapy at baseline.

Table 7: ACR Response in Study PsA-I (Percent of Patients)

Response	Placebo N=162	HUMIRA* N=151
ACR20		
Week 12	14%	58%
Week 24	15%	57%
ACR50		
Week 12	4%	36%
Week 24	6%	39%
ACR70		
Week 12	1%	20%
Week 24	1%	23%

* $p<0.001$ for all comparisons between HUMIRA and placebo

Table 8: Components of Disease Activity in Study PsA-I

	Placebo N=162		HUMIRA* N=151	
Parameter: median	Baseline	24 weeks	Baseline	24 weeks
Number of tender joints[a]	23.0	17.0	20.0	5.0
Number of swollen joints[b]	11.0	9.0	11.0	3.0
Physician global assessment[c]	53.0	49.0	55.0	16.0
Patient global assessment[c]	49.5	49.0	48.0	20.0
Pain[c]	49.0	49.0	54.0	20.0
Disability index (HAQ)[d]	1.0	0.9	1.0	0.4
CRP (mg/dL)[e]	0.8	0.7	0.8	0.2

* $p<0.001$ for HUMIRA vs. placebo comparisons based on median changes

a Scale 0-78

b Scale 0-76

c Visual analog scale; 0=best, 100=worst

d Disability Index of the Health Assessment Questionnaire; 0=best, 3=worst; measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity.

e Normal range: 0-0.287 mg/dL

Similar results were seen in an additional, 12-week study in 100 patients with moderate to severe psoriatic arthritis who had suboptimal response to DMARD therapy as manifested by ≥3 tender joints and ≥3 swollen joints at enrollment.

Radiographic Response

Radiographic changes were assessed in the psoriatic arthritis studies. Radiographs of hands, wrists, and feet were obtained at baseline and Week 24 during the double-blind period when patients were on HUMIRA or placebo and at Week 48 when all patients were on open-label HUMIRA. A modified Total Sharp Score (mTSS), which included distal interphalangeal joints (i.e., not identical to the TSS used for rheumatoid arthritis), was used by readers blinded to treatment group to assess the radiographs.

HUMIRA-treated patients demonstrated greater inhibition of radiographic progression compared to placebo-treated patients and this effect was maintained at 48 weeks (see Table 9).

Table 9: Change in Modified Total Sharp Score in Psoriatic Arthritis

	Placebo N=141	HUMIRA N=133	
	Week 24	Week 24	Week 48
Baseline mean	22.1	23.4	23.4
Mean Change ± SD	0.9 ± 3.1	-0.1 ± 1.7	-0.2 ± 4.9*
* <0.001 for the difference between HUMIRA, Week 48 and Placebo, Week 24 (primary analysis)			

Physical Function Response

In Study PsA-I, physical function and disability were assessed using the HAQ Disability Index (HAQ-DI) and the SF-36 Health Survey. Patients treated with 40 mg of HUMIRA every other week showed greater improvement from baseline in the HAQ-DI score (mean decreases of 47% and 49% at Weeks 12 and 24 respectively) in comparison to placebo (mean decreases of 1% and 3% at Weeks 12 and 24 respectively). At Weeks 12 and 24, patients treated with HUMIRA showed greater improvement from baseline in the SF-36 Physical Component Summary score compared to patients treated with placebo, and no worsening in the SF-36 Mental Component Summary score. Improvement in physical function based on the HAQ-DI was maintained for up to 84 weeks through the open-label portion of the study.

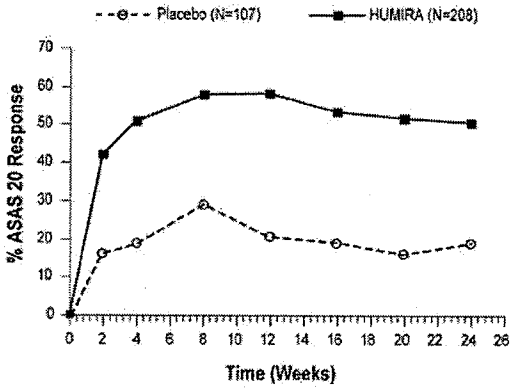
14.3 Ankylosing Spondylitis

The safety and efficacy of HUMIRA 40 mg every other week was assessed in 315 adult patients in a randomized, 24 week double-blind, placebo-controlled study in patients with active ankylosing spondylitis (AS) who had an inadequate response to glucocorticoids, NSAIDs, analgesics, methotrexate or sulfasalazine. Active AS was defined as patients who fulfilled at least two of the following three criteria: (1) a Bath AS disease activity index (BASDAI) score ≥4 cm, (2) a visual analog score (VAS) for total back pain ≥ 40 mm, and (3) morning stiffness ≥ 1 hour. The blinded period was followed by an open-label period during which patients received HUMIRA 40 mg every other week subcutaneously for up to an additional 28 weeks.

Improvement in measures of disease activity was first observed at Week 2 and maintained through 24 weeks as shown in Figure 2 and Table 10.

Responses of patients with total spinal ankylosis (n=11) were similar to those without total ankylosis.

Figure 2: ASAS 20 Response By Visit, Study AS-I



At 12 weeks, the ASAS 20/50/70 responses were achieved by 58%, 38%, and 23%, respectively, of patients receiving HUMIRA, compared to 21%, 10%, and 5% respectively, of patients receiving placebo (p <0.001). Similar responses were seen at Week 24 and were sustained in patients receiving open-label HUMIRA for up to 52 weeks.

A greater proportion of patients treated with HUMIRA (22%) achieved a low level of disease activity at 24 weeks (defined as a value <20 [on a scale of 0 to 100 mm] in each of the four ASAS response parameters) compared to patients treated with placebo (6%).

Table 10: Components of Ankylosing Spondylitis Disease Activity

	Placebo N=107		HUMIRA N=208	
	Baseline mean	Week 24 mean	Baseline mean	Week 24 mean
ASAS 20 Response Criteria*				
Patient's Global Assessment of Disease Activity[a*]	65	60	63	38
Total back pain*	67	58	65	37
Inflammation[b*]	6.7	5.6	6.7	3.6
BASFI[c*]	56	51	52	34
BASDAI[d] score*	6.3	5.5	6.3	3.7
BASMI[e] score*	4.2	4.1	3.8	3.3
Tragus to wall (cm)	15.9	15.8	15.8	15.4
Lumbar flexion (cm)	4.1	4.0	4.2	4.4
Cervical rotation (degrees)	42.2	42.1	48.4	51.6
Lumbar side flexion (cm)	8.9	9.0	9.7	11.7
Intermalleolar distance (cm)	92.9	94.0	93.5	100.8
CRP[f*]	2.2	2.0	1.8	0.6

a Percent of subjects with at least a 20% and 10-unit improvement measured on a Visual Analog Scale (VAS) with 0 = "none" and 100 = "severe"
b mean of questions 5 and 6 of BASDAI (defined in 'd')
c Bath Ankylosing Spondylitis Functional Index
d Bath Ankylosing Spondylitis Disease Activity Index
e Bath Ankylosing Spondylitis Metrology Index
f C-Reactive Protein (mg/dL)
* statistically significant for comparisons between HUMIRA and placebo at Week 24

A second randomized, multicenter, double-blind, placebo-controlled study of 82 patients with ankylosing spondylitis showed similar results.

Patients treated with HUMIRA achieved improvement from baseline in the Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL) score (-3.6 vs. -1.1) and in the Short Form Health Survey (SF-36) Physical Component Summary (PCS) score (7.4 vs. 1.9) compared to placebo-treated patients at Week 24.

14.4 Crohn's Disease

The safety and efficacy of multiple doses of HUMIRA were assessed in adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index (CDAI) $\geq$ 220 and $\leq$ 450) in randomized, double-blind, placebo-controlled studies. Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted, and 79% of patients continued to receive at least one of these medications.

Induction of clinical remission (defined as CDAI < 150) was evaluated in two studies. In Study CD-I, 299 TNF-blocker naïve patients were randomized to one of four treatment groups: the placebo group received placebo at Weeks 0 and 2, the 160/80 group received 160 mg HUMIRA at Week 0 and 80 mg at Week 2, the 80/40 group received 80 mg at Week 0 and 40 mg at Week 2, and the 40/20 group received 40 mg at Week 0 and 20 mg at Week 2. Clinical results were assessed at Week 4.

In the second induction study, Study CD-II, 325 patients who had lost response to, or were intolerant to, previous infliximab therapy were randomized to receive either 160 mg HUMIRA at Week 0 and 80 mg at Week 2, or placebo at Weeks 0 and 2. Clinical results were assessed at Week 4.

Maintenance of clinical remission was evaluated in Study CD-III. In this study, 854 patients with active disease received open-label HUMIRA, 80 mg at week 0 and 40 mg at Week 2. Patients were then randomized at Week 4 to 40 mg HUMIRA every other week, 40 mg HUMIRA every week, or placebo. The total study duration was 56 weeks. Patients in clinical response (decrease in CDAI $\geq$70) at Week 4 were stratified and analyzed separately from those not in clinical response at Week 4.

Induction of Clinical Remission

A greater percentage of the patients treated with 160/80 mg HUMIRA achieved induction of clinical remission versus placebo at Week 4 regardless of whether the patients were TNF blocker naïve (CD-I), or had lost response to or were intolerant to infliximab (CD-II) (see Table 11).

Table 11: Induction of Clinical Remission in Studies CD-I and CD-II (Percent of Patients)

	CD-I		CD-II	
	Placebo N=74	HUMIRA 160/80 mg N=76	Placebo N=166	HUMIRA 160/80 mg N=159
Week 4				
Clinical remission	12%	36%*	7%	21%*
Clinical response	34%	58%**	34%	52%**

Clinical remission is CDAI score < 150; clinical response is decrease in CDAI of at least 70 points.
*p<0.001 for HUMIRA *vs.* placebo pairwise comparison of proportions
**p<0.01 for HUMIRA *vs.* placebo pairwise comparison of proportions

Maintenance of Clinical Remission

In Study CD-III at Week 4, 58% (499/854) of patients were in clinical response and were assessed in the primary analysis. At Weeks 26 and 56, greater proportions of patients who were in clinical response at Week 4 achieved clinical remission in the HUMIRA 40 mg every other week maintenance group compared to patients in the placebo maintenance group (see Table 12). The group that received HUMIRA therapy every week did not demonstrate significantly higher remission rates compared to the group that received HUMIRA every other week.

Table 12: Maintenance of Clinical Remission in CD-III (Percent of Patients)

	Placebo N=170	40 mg HUMIRA every other week N=172
Week 26		
Clinical remission	17%	40%*
Clinical response	28%	54%*
Week 56		
Clinical remission	12%	36%*
Clinical response	18%	43%*

Clinical remission is CDAI score < 150; clinical response is decrease in CDAI of at least 70 points.
*p<0.001 for HUMIRA *vs.* placebo pairwise comparisons of proportions

Of those in response at Week 4 who attained remission during the study, patients in the HUMIRA every other week group maintained remission for a longer time than patients in the placebo maintenance group. Among patients who were not in response by Week 12, therapy continued beyond 12 weeks did not result in significantly more responses.

14.5 Plaque Psoriasis

The safety and efficacy of HUMIRA were assessed in randomized, double-blind, placebo-controlled studies in 1696 adult patients with moderate to severe chronic plaque psoriasis who were candidates for systemic therapy or phototherapy.

Study Ps-I evaluated 1212 patients with chronic plaque psoriasis with ≥10% body surface area (BSA) involvement, Physician's Global Assessment (PGA) of at least moderate disease severity, and Psoriasis Area and Severity Index (PASI) ≥12 within three treatment periods. In period A, patients received placebo or HUMIRA at an initial dose of 80 mg at Week 0 followed by a dose of 40 mg every other week starting at Week 1. After 16 weeks of therapy, patients who achieved at least a PASI 75 response at Week 16, defined as a PASI score improvement of at least 75% relative to baseline, entered period B and received open-label 40

mg HUMIRA every other week. After 17 weeks of open label therapy, patients who maintained at least a PASI 75 response at Week 33 and were originally randomized to active therapy in period A were re-randomized in period C to receive 40 mg HUMIRA every other week or placebo for an additional 19 weeks. Across all treatment groups the mean baseline PASI score was 19 and the baseline Physician's Global Assessment score ranged from "moderate" (53%) to "severe" (41%) to "very severe" (6%).

Study Ps-II evaluated 99 patients randomized to HUMIRA and 48 patients randomized to placebo with chronic plaque psoriasis with ≥10% BSA involvement and PASI ≥12. Patients received placebo, or an initial dose of 80 mg HUMIRA at Week 0 followed by 40 mg every other week starting at Week 1 for 16 weeks. Across all treatment groups the mean baseline PASI score was 21 and the baseline PGA score ranged from "moderate" (41%) to "severe" (51%) to "very severe" (8%).

Studies Ps-I and II evaluated the proportion of patients who achieved "clear" or "minimal" disease on the 6-point PGA scale and the proportion of patients who achieved a reduction in PASI score of at least 75% (PASI 75) from baseline at Week 16 (see Table 13 and 14).

Additionally, Study Ps-I evaluated the proportion of subjects who maintained a PGA of "clear" or "minimal" disease or a PASI 75 response after Week 33 and on or before Week 52.

Table 13: Efficacy Results at 16 Weeks in Study Ps-I
Number of Patients (%)

	HUMIRA 40 mg every other week N = 814	Placebo N = 398
PGA: Clear or minimal*	506 (62%)	17 (4%)
PASI 75	578 (71%)	26 (7%)
*Clear = no plaque elevation, no scale, plus or minus hyperpigmentation or diffuse pink or red coloration Minimal = possible but difficult to ascertain whether there is slight elevation of plaque above normal skin, plus or minus surface dryness with some white coloration, plus or minus up to red coloration		

Table 14: Efficacy Results at 16 Weeks in Study Ps-II
Number of Patients (%)

	HUMIRA 40 mg every other week N = 99	Placebo N = 48
PGA: Clear or minimal*	70 (71%)	5 (10%)
PASI 75	77 (78%)	9 (19%)
*Clear = no plaque elevation, no scale, plus or minus hyperpigmentation or diffuse pink or red coloration Minimal = possible but difficult to ascertain whether there is slight elevation of plaque above normal skin, plus or minus surface dryness with some white coloration, plus or minus up to red coloration		

Additionally, in Study Ps-I, subjects on HUMIRA who maintained a PASI 75 were re-randomized to HUMIRA (N = 250) or placebo (N = 240) at Week 33. After 52 weeks of treatment with HUMIRA, more patients on HUMIRA maintained efficacy when compared to subjects who were re-randomized to placebo based on maintenance of PGA of "clear" or "minimal" disease (68% vs. 28%) or a PASI 75 (79% vs. 43%).

15 REFERENCES

1. National Cancer Institute. Surveillance, Epidemiology, and End Results Database (SEER) Program. SEER Incidence Crude Rates, 11 Registries, 1993-2001.

16 HOW SUPPLIED/STORAGE AND HANDLING

HUMIRA® (adalimumab) is supplied in prefilled syringes as a preservative-free, sterile solution for subcutaneous administration. The following packaging configurations are available.

- **HUMIRA Pen Carton**

HUMIRA is dispensed in a carton containing two alcohol preps and two dose trays. Each dose tray consists of a single-use pen, containing a 1 mL prefilled glass syringe with a fixed 27 gauge ½ inch needle, providing 40 mg (0.8 mL) of HUMIRA. The NDC number is 0074-4339-02.

- **HUMIRA Pen – Crohn's Disease Starter Package**

HUMIRA is dispensed in a carton containing 6 alcohol preps and 6 dose trays (Crohn's Disease Starter Package). Each dose tray consists of a single-use pen, containing a 1 mL prefilled glass syringe with a fixed 27 gauge ½ inch needle, providing 40 mg (0.8 mL) of HUMIRA. The NDC number is 0074-4339-06.

- **Prefilled Syringe Carton – 40 mg**

HUMIRA is dispensed in a carton containing two alcohol preps and two dose trays. Each dose tray consists of a single-use, 1 mL prefilled glass syringe with a fixed 27 gauge ½ inch needle, providing 40 mg (0.8 mL) of HUMIRA. The NDC number is 0074-3799-02.

- **Storage and Stability**

Do not use beyond the expiration date on the container. HUMIRA must be refrigerated at 2 to 8° C (36 to 46° F). DO NOT FREEZE. Protect the prefilled syringe from exposure to light. Store in original carton until time of administration.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.3)

17.1 Patient Counseling

Patients should be advised of the potential benefits and risks of HUMIRA. Physicians should instruct their patients to read the Medication Guide before starting HUMIRA therapy and to reread each time the prescription is renewed.

- **Immunosuppression**

Inform patients that HUMIRA may lower the ability of their immune system to fight infections. Instruct the patient of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis and reactivation of hepatitis B virus infections.

Patients should be counseled about the risk of lymphoma and other malignancies while receiving HUMIRA.

- **Allergic Reactions**

Patients should be advised to seek immediate medical attention if they experience any symptoms of severe allergic reactions. Advise latex-sensitive patients that the needle cap of the prefilled syringe contains latex.

- **Other Medical Conditions**

Advise patients to report any signs of new or worsening medical conditions such as heart disease, neurological disease, or autoimmune disorders. Advise patients to report any symptoms suggestive of a cytopenia such as bruising, bleeding, or persistent fever.

17.2 Instruction on Injection Technique

The first injection should be performed under the supervision of a qualified health care professional. If a patient or caregiver is to administer HUMIRA, he/she should be instructed in injection techniques and their ability to inject subcutaneously should be assessed to ensure the proper administration of HUMIRA *[see Patient Counseling Information (17.3)]*.

A puncture-resistant container for disposal of needles and syringes should be used. Patients or caregivers should be instructed in the technique as well as proper syringe and needle disposal, and be cautioned against reuse of these items.

17.3 FDA-Approved Patient Labeling

MEDICATION GUIDE
HUMIRA® (HU-MARE-AH)
(adalimumab)

Read the Medication Guide that comes with HUMIRA before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment with HUMIRA.

What is the most important information I should know about HUMIRA?

HUMIRA is a medicine that affects your immune system. HUMIRA can lower the ability of your immune system to fight infections. **Serious infections have happened in patients receiving HUMIRA. These infections include TB (tuberculosis) and infections caused by viruses, fungi or bacteria that have spread throughout the body. Some patients have died from these infections.**

HUMIRA may not be right for you. Before starting HUMIRA, tell your doctor if you:

- think you have any kind of infection, even if it is very minor (such as an open sore).
- are being treated for an infection
- have signs of an infection, such as a fever, cough, or flu-like symptoms
- have warm, red, or painful skin
- get a lot of infections or have infections that keep coming back
- have or had hepatitis B infection. If you are a chronic carrier of the virus that causes hepatitis B, taking HUMIRA could cause the hepatitis B virus to become an active infection again.
- have TB, or have been in close contact with someone who has TB. Your doctor should test you for TB before starting HUMIRA. If your doctor prescribes any medicine for the treatment of TB, you should start taking it before starting HUMIRA and take the full course of TB medicine prescribed.
- have lived in an area where TB or histoplasmosis is common. If you do not know if you have lived in an area where TB or histoplasmosis is common, ask your doctor.
- were born in, lived in, or traveled to countries where there is more risk for getting TB. Ask your doctor if you are not sure.
- take the medicine Kineret (anakinra). You may have a higher chance for serious infections and a low white blood cell count when taking HUMIRA with Kineret.
- are scheduled to have major surgery

After starting HUMIRA, call your doctor right away if you get an infection, or any sign of an infection, including:

- a fever
- feel very tired
- a cough
- flu-like symptoms
- warm, red, or painful skin
- open sores on your body

HUMIRA can make you more likely to get infections or make any infection that you may have worse.

What is HUMIRA?

HUMIRA is a medicine called a Tumor Necrosis Factor (TNF) blocker. HUMIRA is used in adults to:

- Reduce the signs and symptoms of:
  - **moderate to severe rheumatoid arthritis (RA)** in adults. HUMIRA can be used alone or with methotrexate or with certain other medicines. HUMIRA may prevent further damage to your bones and joints and may help your ability to perform daily activities.
  - **psoriatic arthritis (PsA).** HUMIRA can be used alone or with certain other medicines. HUMIRA may prevent further damage to your bones and joints and may help your ability to perform daily activities.
  - **ankylosing spondylitis (AS)**
  - **moderate to severe Crohn's disease (CD)** in adults who have not responded well to other treatments.
- **Treat moderate to severe chronic (lasting a long time) plaque psoriasis (Ps)** in adults who have the condition in many areas of their body and who may benefit from taking injections or pills (systemic therapy) or phototherapy (treatment using ultraviolet light alone or with pills).

People with these diseases have too much of a protein called tumor necrosis factor (TNF), in the affected areas of the body. HUMIRA can block the bad effects of TNF in those affected areas, but it can also lower the ability of the immune system to fight infections. See **"What is the most important information I should know about HUMIRA?"** and **"What are the possible side effects of HUMIRA?"**

HUMIRA has not been studied in children.

What should I tell my doctor before taking HUMIRA?

Before starting HUMIRA, tell your doctor about all of your health conditions, including if you:

- **have an infection. See "What is the most important information I should know about HUMIRA?"**
- have any numbness or tingling or have a disease that affects your nervous system such as multiple sclerosis or Guillain-Barré syndrome.
- have heart failure or other heart conditions. If you have heart failure, it may get worse while you are taking HUMIRA.
- have recently received or are scheduled to receive a vaccine. Patients receiving HUMIRA should not receive live vaccines.
- are allergic to rubber or latex. The needle cover on the prefilled syringe contains dry natural rubber. Tell you doctor if you have any allergies to rubber or latex.
- are allergic to HUMIRA or to any of its ingredients. See the end of this Medication Guide for a list of ingredients in HUMIRA.

Tell your doctor if you are pregnant, planning to become pregnant, or breastfeeding. HUMIRA should only be used during a pregnancy if needed. Women who are breastfeeding should talk to their doctor about whether or not to use HUMIRA.

Pregnancy Registry: Abbott Laboratories has a registry for pregnant women who take HUMIRA. The purpose of this registry is to check the health of the pregnant mother and her child. Talk to your doctor if you are pregnant and contact the registry at 1-877-311-8972.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. Especially, tell your doctor if you take Kineret (anakinra). You may have a higher chance for serious infections and a low white blood cell count when taking HUMIRA with Kineret. Also, tell your doctor if you are taking other medicines that suppress the immune system.

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist each time you get a new medicine.

How should I take HUMIRA?

See the section, **"How do I prepare and give an injection of HUMIRA?"** at the end of this Medication Guide for complete instructions for use.

- HUMIRA is given by an injection under the skin. Your doctor will tell you how often to take an injection of HUMIRA. This is based on your condition to be treated. **Do not inject HUMIRA more often than prescribed.**
- Make sure you have been shown how to inject HUMIRA before you do it yourself. You can call your doctor or 1-800-4HUMIRA (448-6472) if you have any questions about giving yourself an injection. Someone you know can also help you with your injection.
- If you take more HUMIRA than you were told to take, call your doctor.
- Do not miss any doses of HUMIRA. If you forget to take HUMIRA, inject a dose as soon as you remember. Then, take your next dose at your regular scheduled time. This will put you back on schedule. To help you remember when to take HUMIRA, you can mark your calendar ahead of time with the stickers provided in the back of the Medication Guide.

What are the possible side effects with HUMIRA?

Serious side effects, which sometimes lead to death, have happened in patients taking HUMIRA, including:

- **Serious infections.** See **"What is the most important information I should know about HUMIRA?"**

  Your doctor will examine you for TB and perform a test to see if you have TB. If your doctor feels that you are at risk for TB, you may be treated with medicine for TB before you begin treatment with HUMIRA and during treatment with HUMIRA. Even if your TB test is negative your doctor should carefully monitor you for TB infections while you are taking HUMIRA. Patients who had a negative TB skin test before receiving HUMIRA have developed active TB. Tell your doctor if you have any of the following symptoms while taking or after taking HUMIRA:

  - cough that does not go away
  - low grade fever
  - weight loss
  - loss of body fat and muscle (wasting)

- **Certain types of Cancer.**
  - There have been cases of certain kinds of cancer, in patients taking HUMIRA or other TNF blockers.

- Some patients receiving HUMIRA have developed types of cancer called non-melanoma skin cancer (basal cell cancer and squamous cell cancer of the skin), which are generally not life-threatening if treated. Tell your doctor if you have a bump or open sore that doesn't heal.
- Patients with RA, especially more serious RA, may have a higher chance for getting a kind of cancer called lymphoma.

- **Allergic reactions.** Signs of a serious allergic reaction include a skin rash, a swollen face, or trouble breathing.
- **Hepatitis B virus reactivation in patients who carry the virus in their blood.** In some cases patients have died as a result of hepatitis B virus being reactivated. Your doctor should monitor you carefully during treatment with HUMIRA if you carry the hepatitis B virus in your blood. Tell your doctor if you have any of the following symptoms:
  - feel unwell
  - poor appetite
  - tiredness (fatigue)
  - fever, skin rash, or joint pain
- **Nervous system problems.** Signs and symptoms of a nervous system problem include: numbness or tingling, problems with your vision, weakness in your arms or legs, and dizziness.
- **Blood problems.** Your body may not make enough of the blood cells that help fight infections or help to stop bleeding. Symptoms include a fever that does not go away, bruising or bleeding very easily, or looking very pale.
- **New heart failure or worsening of heart failure you already have.** Symptoms include shortness of breath or swelling of your ankles or feet or sudden weight gain.
- **Immune reactions including a lupus-like syndrome.** Symptoms include chest discomfort or pain that does not go away, shortness of breath, joint pain, or a rash on your cheeks or arms that gets worse in the sun. Symptoms may go away when you stop HUMIRA.

Call your doctor or get medical care right away if you develop any of the above symptoms. Your treatment with HUMIRA may be stopped.

Common side effects with HUMIRA include:

- **Injection site reactions** such as redness, rash, swelling, itching, or bruising. These symptoms usually will go away within a few days. If you have pain, redness or swelling around the injection site that doesn't go away within a few days or gets worse, call your doctor right away.
- **Upper respiratory infections** (including sinus infections)
- **Headaches**
- **Rash**
- **Nausea**

These are not all the possible side effects with HUMIRA. Tell your doctor if you have any side effect that bothers you or that does not go away. Ask your doctor or pharmacist for more information.

How do I store HUMIRA?

- Store HUMIRA in a refrigerator at 36 to 46°F (2°C to 8°C) in the original container until it is used. Protect from light. **Do not freeze HUMIRA.** Refrigerated HUMIRA remains okay to use until the expiration date printed on the prefilled syringe or Pen. If you need to take HUMIRA with you, such as when traveling, store it in a cool carrier with an ice pack and protect it from light. If your HUMIRA has been frozen, do not use it, even after it has thawed. Do not use a Pen or prefilled syringe if the liquid is cloudy, discolored, or has flakes or particles in it. For additional information or questions, you can call 1-800-4HUMIRA (488-6472).
- Do not drop or crush HUMIRA. The prefilled syringe is glass.
- **Keep HUMIRA, injection supplies, and all other medicines out of the reach of children.**

General information about HUMIRA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use HUMIRA for a condition for which it was not prescribed. Do not give HUMIRA to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about HUMIRA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about HUMIRA that was written for healthcare professionals.

For more information go to www.HUMIRA.com or you can enroll in a patient support program by calling 1-800-4HUMIRA (448-6472).

What are the ingredients in HUMIRA?

Active ingredient: adalimumab
Inactive ingredients: sodium phosphate, sodium citrate, citric acid, mannitol, and polysorbate 80.

Patient Instructions for Use

What do I need to do to prepare and give an injection of HUMIRA?

HUMIRA comes as:

1. a single-use pen (HUMIRA PEN) containing a prefilled syringe
2. a single-use prefilled syringe (HUMIRA)

Follow the directions below for your dose form.

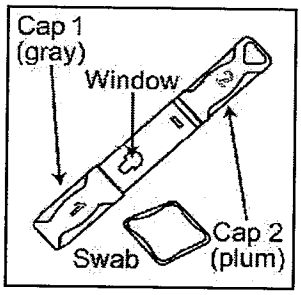
IF YOU ARE USING THE HUMIRA PEN

1) Setting up for an injection

- Find a clean flat surface.
- Do not use if the seals on top and bottom of carton are broken or missing. Contact your pharmacist if the seals are broken.
- Take one dose tray containing a HUMIRA Pen from the refrigerator. Do not use a Pen that has been frozen or if it has been left in direct sunlight.

You will need the following items for each dose:

- 1 HUMIRA Pen
- 1 alcohol prep (swab)
- 1 cotton ball or gauze pad (not included in your HUMIRA box)



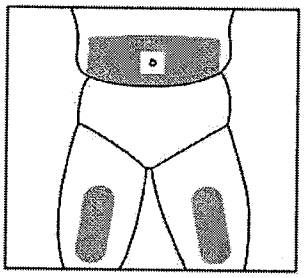
If you do not have all of the items you need to give yourself an injection, call your pharmacist. Use only the items provided in the box your HUMIRA comes in.

- Check and make sure the name HUMIRA appears on the dose tray and Pen label.
- Check the expiration date on the dose tray label and the Pen label to make sure the date has not passed. Do not use a Pen if the date has passed.
- Have a special sharps (puncture proof) container nearby for disposing of the used Pen.

For your protection, it is important that you follow these instructions.

2) Choosing and preparing an injection site

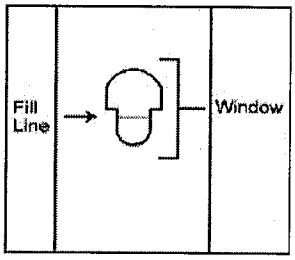
- Wash your hands well



- Choose a site on the front of your thighs or your stomach area (abdomen). If you choose your abdomen, you should avoid the area 2 inches around your belly button (navel).
  - Choose a different site each time you give yourself an injection. Each new injection should be given at least one inch from a site you used before. **Never** inject into areas where the skin is tender, bruised, red or hard or where you have scars or stretch marks.
  - If you have psoriasis, you should try not to inject directly into any raised, thick, red or scaly skin patches or lesions.
  - You may find it helpful to keep notes on the location of your injection sites.
- Wipe the site where HUMIRA is to be injected with an alcohol prep (swab), using a circular motion. Do **not** touch this area again until you are ready to inject.

3) How to prepare your HUMIRA dose for injection with a HUMIRA Pen

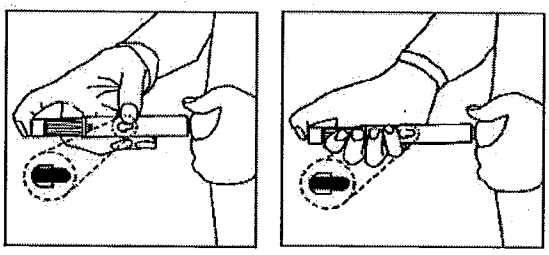
- Hold the Pen with the gray cap pointing up. Check the solution through the windows on the side of the Pen to make sure the liquid is clear and colorless. Do not use a Pen if the liquid is cloudy or discolored or has flakes or particles in it. Do not use if frozen.



- Turn the Pen over and hold the Pen with the gray cap pointed down. Check to make sure that the amount of liquid in the Pen is the same or close to the fill line seen through the window. The fill line represents a full dose of the product. The top of the liquid may be curved. If the Pen does not have the full amount of liquid, **do not use that pen.** Call your pharmacist.

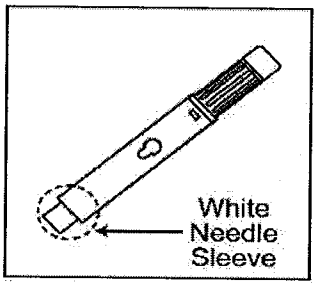
4) Injecting HUMIRA

- Hold the Pen with one hand. With your other hand, remove the gray cap (1) and discard cap. Pull the cap straight off. Do not twist the cap. Check that the small gray needle cover of the syringe has come off with the cap. After removal, the needle cover is held in the cap. Do not touch the needle. The white needle sleeve, which covers the needle, can now be seen. **Do not put the gray cap (1) back on** or you may damage the needle. Do not drop or crush the product as it contains a glass syringe that may break.
- Remove the plum colored safety cap (2) to expose the plum colored push button at the top. Pull the cap straight off. Do not twist the cap. The Pen is now ready to use. Please note that the Pen is activated after removing the plum colored safety cap 2 and that pressing the button under the plum colored safety cap 2 will release the medicine from the syringe. Do not press the button until you are ready to inject HUMIRA. **Do not put the plum colored cap (2) back on the pen as this could cause medicine to come out of the syringe.**
- Hold the Pen so that the window can be seen.
- With your free hand, gently squeeze an area of the cleaned skin at the injection site. You will inject into this raised area of skin.
- Place the white end of the Pen straight (a 90° angle) and flat against the raised area of skin. Place the Pen so that it will not inject the needle into your fingers that are holding the raised skin.



- With your first (index) finger, press the plum colored button to begin the injection. You may also use your thumb to press the plum colored button to begin the injection. Try not to cover the window. You will hear a 'click' when you press the button, which means the start of the injection. Keep pressing the button and continue to hold the Pen against the raised skin until all of the medicine is injected. This can take up to 10 seconds. It is important to keep holding the pen against the raised skin of your injection site for the whole time.

- You will know that the injection has finished when the yellow marker appears fully in the window view and stops moving.



- When the injection is finished, pull the Pen from the skin. The white needle sleeve will move to cover the needle tip.
- Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. Do **not** rub the injection site. You may have slight bleeding. This is normal.
- Dispose of the Pen right away into your special sharps container.
- Do not try to touch the needle. The white needle sleeve is there to prevent you from touching the needle. (See **"How Do I Dispose of Syringes and Needles?")**

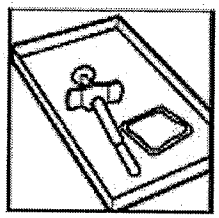
IF YOU ARE USING THE PREFILLED SYRINGE

1) Setting up for an injection

- Find a clean flat surface.
- Do not use if the seals on top and bottom of carton are broken or missing. Contact your pharmacist if the seals are broken.
- Take one dose tray containing a prefilled syringe of HUMIRA from the refrigerator. Do not use a prefilled syringe that has been frozen or if it has been left in direct sunlight.

  You will need the following items for each dose:

  - A dose tray containing a prefilled syringe of HUMIRA with a fixed needle
  - 1 alcohol prep (swab)
  - 1 cotton ball or gauze pad (not included in your HUMIRA box)



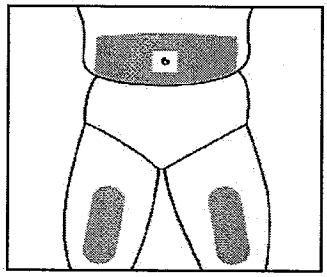
If you do not have all of the items you need to give yourself an injection, call your pharmacist. Use only the items provided in the box your HUMIRA comes in.

- Check and make sure the name HUMIRA appears on the dose tray and prefilled syringe label.
- Check the expiration date on the dose tray label and prefilled syringe to make sure the date has not passed. Do not use a prefilled syringe if the date has passed.

- Make sure the liquid in the prefilled syringe is clear and colorless. Do not use a prefilled syringe if the liquid is cloudy or discolored or has flakes or particles in it.
- Have a special sharps (puncture proof) container nearby for disposing of used needles and syringes.

For your protection, it is important that you follow these instructions.

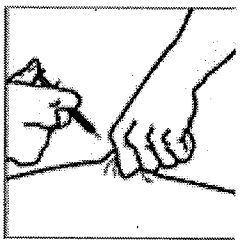
2) **Choosing and preparing an injection site**



- Wash your hands well
- Choose a site on the front of your thighs or your stomach area (abdomen). If you choose your abdomen, you should avoid the area 2 inches around your belly button (navel).
  - Choose a different site each time you give yourself an injection. Each new injection should be given at least one inch from a site you used before. **Never** inject into areas where the skin is tender, bruised, red or hard or where you have scars or stretch marks.
  - If you have psoriasis, you should try not to inject directly into any raised, thick, red or scaly skin patches or lesions.
  - You may find it helpful to keep notes on the location of your injection sites.
- Wipe the site where HUMIRA is to be injected with an alcohol prep (swab), using a circular motion. Do **not** touch this area again until you are ready to inject.

3) **How to prepare your HUMIRA dose for injection with a Prefilled Syringe**

- Hold the syringe upright with the needle facing down. Check to make sure that the amount of liquid in the syringe is the same or close to the 0.8 mL line shown on the prefilled syringe. The top of the liquid may be curved. If the syringe does not have the correct amount of liquid, **do not use that syringe**. Call your pharmacist.
- Remove the needle cover taking care not to touch the needle with your fingers or allow it to touch any surface.
- Turn the syringe so the needle is facing up and slowly push the plunger in to push the air in the syringe out through the needle. If a small drop of liquid comes out of the needle that is okay. Do not shake the syringe.



4) **Injecting HUMIRA**

- With your other hand, gently squeeze an area of the cleaned area of skin and hold it firmly. You will inject into this raised area of skin. Hold the syringe like a pencil at about a 45° angle (see picture) to the skin.
- With a quick, short, "dart-like" motion, push the needle into the skin.
- After the needle is in, let go of the skin. Pull back slightly on the plunger. If blood appears in the syringe it means that you have entered a blood vessel. Do not inject HUMIRA. Pull the needle out of the skin and repeat the steps to choose and clean a new injection site. **Do not** use the same syringe. Dispose of it in your special sharps container. If no blood appears, slowly push the plunger all the way in until all of the HUMIRA is injected.
- When the syringe is empty, remove the needle from the skin keeping it at the same angle it was when it was pushed into the skin.
- Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. Do **not** rub the injection site. You may have slight bleeding. This is normal.
- Dispose of the syringe right away into your special sharps container. (See **"How Do I Dispose of Syringes and Needles?")**

How Do I Dispose of Syringes and Needles?

You should always check with your doctor's office for instructions on how to dispose of used needles and syringes. You should follow any special state or local laws regarding the disposal of needles and syringes. **Do not throw the needle or syringe in the household trash or recycle trash.**

- Place the used needles and syringes in a container made specially for disposing of used syringes and needles (called a "Sharps" container), or a hard plastic container with a screw-on cap or metal container with a plastic lid labeled "Used Syringes". Do not use glass or clear plastic containers.
- **Always keep the container out of the reach of children.**
- When the container is about two-thirds full, tape the cap or lid down so it does not come off and dispose of it as instructed by your doctor, nurse or pharmacist. **Do not throw the container in the household trash or recycle trash.**
- Used alcohol pads may be placed in the trash, unless otherwise instructed by your doctor, nurse or pharmacist. The dose tray and cover may be placed in your recycle trash.

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