HUMIRA®
(adalimumab)

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

WARNINGS:

See full prescribing information for complete boxed warning.

SERIOUS INFECTIONS (5.1, 6.1)

• Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens.
• HUMIRA should be discontinued if a patient develops a serious infection or sepsis during treatment.
• 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.

MALIGNANCY (5.2)

• Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which HUMIRA is a member.
• Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have occurred in adolescent and young adults with inflammatory bowel disease treated with TNF blockers including HUMIRA.

RECENT MAJOR CHANGES

Boxed Warning 3/2011
Dosage and Administration, Crohn’s Disease (2.3) 3/2011
Dosage and Administration, Monitoring to Assess Safety (2.5) 3/2011
Warnings and Precautions, Serious Infections (5.1) 3/2011
Warnings and Precautions, Malignancies (5.2) 3/2011
Warnings and Precautions, Neurologic Reactions (5.5) 7/2010
Warnings and Precautions, Use with Abatacept (5.11) 3/2011

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 RA.

Juvenile Idiopathic Arthritis (JIA) (1.2)
• Reducing signs and symptoms of moderately to severely active polyarticular JIA in pediatric patients 4 years of age and older.

Psoriatic Arthritis (PsA) (1.3)
• Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.

Ankylosing Spondylitis (AS) (1.4)
• Reducing signs and symptoms in adult patients with active AS.

Crohn’s Disease (CD) (1.5)
• 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 (Ps) (1.6)
• 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.

DOSEAGE 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.

Plaque Psoriasis (2.4)
• 80 mg initial dose, followed by 40 mg every other week starting one week after initial dose.

DOSEAGE 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)
• 20 mg/0.4 mL in a single-use prefilled glass syringe (3)

CONTRAINDICATIONS

• None (4)

DRUG INTERACTIONS

• Abatacept – increased risk of serious infection (5.1, 5.11, 7.2)
• Anakinra – increased risk of serious infection (5.1, 5.7, 7.2)
• Live vaccines – should not be given with HUMIRA (5.10, 7.3)
• 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 antiviral 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

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 Medication Guide

Revised: 03/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

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The risks and benefits of treatment with HUMIRA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy. [See Warnings and Precautions (5.1) and Adverse Reactions (6.1)]

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which HUMIRA is a member [See Warnings and Precautions (5.2)]. Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases has occurred in patients with Crohn’s disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants.

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 non-biologic disease-modifying anti-rheumatic drugs (DMARDs).

1.2 Juvenile Idiopathic Arthritis

HUMIRA is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in pediatric patients 4 years of age and older. HUMIRA can be used alone or in combination with methotrexate.

1.3 Psoriatic Arthritis

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

1.4 Ankylosing Spondylitis

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

1.5 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.

1.6 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 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 (RA), psoriatic arthritis (PsA), or ankylosing spondylitis (AS) is 40 mg administered every other week. Methotrexate (MTX), other nonbiologic DMARDs, glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), and/or analgesics may be continued during treatment with
HUMIRA. In the treatment of RA, some patients not taking concomitant MTX may derive additional benefit from increasing the dosing frequency of HUMIRA to 40 mg every week.

2.2 Juvenile Idiopathic Arthritis

The recommended dose of HUMIRA for pediatric patients 4 to 17 years of age with polyarticular juvenile idiopathic arthritis (JIA) is based on weight as shown below. MTX, glucocorticoids, NSAIDs, and/or analgesics may be continued during treatment with HUMIRA.

<table>
<thead>
<tr>
<th>Pediatric Patients (4 to 17 years)</th>
<th>Dose</th>
</tr>
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<tbody>
<tr>
<td>15 kg (33 lbs) to &lt;30 kg (66 lbs)</td>
<td>20 mg every other week (20 mg Prefilled Syringe)</td>
</tr>
<tr>
<td>≥30 kg (66 lbs)</td>
<td>40 mg every other week (HUMIRA Pen or 40 mg Prefilled Syringe)</td>
</tr>
</tbody>
</table>

Limited data are available for HUMIRA treatment in pediatric patients with a weight below 15 kg.

2.3 Crohn’s Disease

The recommended HUMIRA dose regimen for adult patients with Crohn’s disease is 160 mg initially on 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 and/or corticosteroids may be continued during treatment with HUMIRA. Azathioprine, 6-mercaptopurine (6-MP) [see Warnings and Precautions (5.2)] or MTX may be continued during treatment with HUMIRA if necessary. The use of HUMIRA in Crohn’s disease beyond one year has not been evaluated in controlled clinical studies.

2.4 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.

2.5 Monitoring to Assess Safety

Prior to initiating HUMIRA and periodically during therapy, patients should be evaluated for tuberculosis and for latent infection [see Warnings and Precautions (5.1)].

2.6 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 Patient Instructions for Use [see Patient Instructions for Use].

Patients (15 kg to <30 kg) using the pediatric pre-filled syringe, or their caregivers, should be instructed to inject the full amount in the syringe (0.4 mL), which provides 20 mg of HUMIRA, according to the directions provided in the Patient Instructions for Use. 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 (see also Boxed WARNINGS)

5.1 Serious Infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens have been reported in patients receiving TNF-blockers including HUMIRA. Among opportunistic infections, tuberculosis, histoplasmosis, aspergillosis, candidiasis, coccidioidomycosis, listeriosis, and pneumocystosis were the most commonly reported. Patients have frequently presented with disseminated rather than localized disease, and were often taking concomitant immunosuppressants such as methotrexate or corticosteroids with HUMIRA. The concomitant use of a TNF blocker and abatacept or anakinra was associated with a higher risk of serious infections in patients with rheumatoid arthritis (RA); therefore, the concomitant use of HUMIRA and these biologic products is not recommended in the treatment of patients with RA [see Warnings and Precautions (5.7, 5.11) and Drug Interactions (7.2)].

Treatment with HUMIRA should not be initiated in patients with an active infection, including localized infections. The risks and benefits of treatment should be considered prior to initiating therapy in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving HUMIRA, including patients who have previously received treatment for latent or active tuberculosis. Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating HUMIRA and periodically during therapy.

Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy. Induration of 5 mm or greater with tuberculin skin testing should be considered a positive test result when assessing if treatment for latent tuberculosis is needed prior to initiating HUMIRA, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG).

Anti-tuberculosis therapy should also 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, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Tuberculosis should be strongly considered in patients who develop a new infection during HUMIRA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with HUMIRA.

HUMIRA should be discontinued if a patient develops a serious infection or sepsis. A patient who develops a new infection during treatment with HUMIRA should be closely monitored, undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and appropriate antimicrobial therapy should be initiated.

For patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy.
5.2 Malignancies

The risks and benefits of TNF-blocker treatment including HUMIRA should be considered prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing a TNF blocker in patients who develop a malignancy.

**Malignancies in Adults**

In the controlled portions of clinical trials of some TNF-blockers, including HUMIRA, more cases of malignancies have been observed among TNF-blocker-treated adult patients compared to control-treated adult patients. During the controlled portions of 32 global HUMIRA clinical trials in adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn’s disease (CD), and plaque psoriasis (Ps), malignancies, other than non-melanoma (basal cell and squamous cell) skin cancer, were observed at a rate (95% confidence interval) of 0.6 (0.38, 0.93) per 100 patient-years among 6694 HUMIRA-treated patients versus a rate of 0.5 (0.28, 1.05) per 100 patient-years among 3749 control-treated patients (median duration of treatment of 4 months for HUMIRA-treated patients and 4 months for control-treated patients). In 45 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD and Ps, the most frequently observed malignancies, other than lymphoma and NMSC, were breast, colon, prostate, lung, and melanoma. The malignancies in HUMIRA-treated patients in the controlled and uncontrolled portions of the studies were similar in type and number to what would be expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).

In controlled trials of other TNF blockers in adult patients at higher risk for malignancies (i.e., patients with COPD with a significant smoking history and cyclophosphamide-treated patients with Wegener’s granulomatosis), a greater portion of malignancies occurred in the TNF blocker group compared to the control group.

**Non-Melanoma Skin Cancer**

During the controlled portions of 32 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, and Ps, the rate (95% confidence interval) of NMSC was 0.7 (0.50, 1.11) per 100 patient-years among HUMIRA-treated patients and 0.2 (0.06, 0.56) per 100 patient-years among control-treated patients. All patients, and in particular patients with a medical history of prior prolonged immunosuppressant therapy or psoriasis patients with a history of PUVA treatment should be examined for the presence of NMSC prior to and during treatment with HUMIRA.

**Lymphoma and Leukemia**

In the controlled portions of clinical trials of all the TNF-blockers in adults, more cases of lymphoma have been observed among TNF-blocker-treated patients compared to control-treated patients. In the controlled portions of 32 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, and Ps, 3 lymphomas occurred among 6694 HUMIRA-treated patients versus 1 among 3749 control-treated patients. In 45 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD and Ps, with a median duration of approximately 0.6 years, including 22,026 patients and over 32,000 patient-years of HUMIRA, the observed rate of lymphomas was approximately 0.11 per 100 patient-years. This is approximately 3-fold higher than expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race). Rates of lymphoma in clinical trials of HUMIRA cannot be compared to rates of lymphoma in clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. Patients with RA and other chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of a TNF blocker. Post-marketing cases of acute and chronic leukemia have been reported in association with TNF-blocker use in RA and other indications. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

**Malignancies in Pediatric Patients and Young Adults**

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers (initiation of therapy ≤ 18 years of age), of which HUMIRA is a member. Approximately half the cases were lymphomas, including Hodgkin’s and non-Hodgkin’s lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous postmarketing reports.

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases has occurred in patients with Crohn’s disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with the immunosuppressants azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants.

5.3 Hypersensitivity Reactions

In postmarketing experience, anaphylaxis and angioedematous 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 in adults, 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 being at risk for 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 central nervous system demyelinating disease, including multiple sclerosis (MS), and peripheral demyelinating disease, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of HUMIRA in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders.

5.6 Hematologic 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. 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

Concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocker, was associated with a greater proportion of serious infections and neutropenia and no added benefit compared with the TNF-blocker alone in patients with RA. Therefore, the combination of HUMIRA and anakinra is not recommended [see Drug Interactions (7.2)].

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 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 antibodies to pneumonia antigens 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.

It is recommended that juvenile idiopathic arthritis patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating HUMIRA therapy. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines.

5.11 Use with Abatacept

In controlled trials, the concurrent administration of TNF-blockers and abatacept was associated with a greater proportion of serious infections than the use of a TNF-blocker alone; the combination therapy, compared to the use of a TNF-blocker alone, has not demonstrated improved clinical benefit in the treatment of RA. Therefore, the combination of abatacept with TNF-blockers including HUMIRA is not recommended [see Drug Interactions (7.2)].

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

The most serious adverse reactions were:

- Serious Infections [see Warnings and Precautions (5.1)]
- Malignancies [see Warnings and Precautions (5.2)]

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.

6.2 Infections

In the controlled portions of the 32 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD and Ps, the rate of serious infections was 4.7 per 100 patient-years in 6694 HUMIRA-treated patients versus a rate of 2.7 per 100 patient-years in 3749 control-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)].

6.3 Tuberculosis and Opportunistic Infections

In 45 global controlled and uncontrolled clinical trials in RA, PsA, AS, CD and Ps that included 22,026 HUMIRA-treated patients, the rate of reported active tuberculosis was 0.22 per 100 patient-years and the rate of positive PPD conversion was 0.07 per 100 patient-years. In a subgroup of 8940 U.S. and Canadian HUMIRA-treated patients, the rate of reported active TB was 0.07 per 100 patient-years and the rate of positive PPD conversion was 0.06 per 100 patient-years. These trials included reports of miliary, lymphatic, peritoneal, and pulmonary TB. Most of the TB cases occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease. In these global clinical trials, cases of serious opportunistic infections have been reported at an overall rate of 0.07 per 100 patient-years. Some cases of serious opportunistic infections and TB have been fatal [see Warnings and Precautions (5.1)].

6.4 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.

6.5 Liver Enzyme Elevations

There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers. In controlled Phase 3 trials of HUMIRA (40 mg SC every other week) in patients with RA, PsA, and AS with control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.5% of HUMIRA-treated patients and 1.5% of control-treated patients. Since many of these patients in these trials were also taking medications that cause liver enzyme elevations (e.g., NSAIDS, MTX), the relationship between HUMIRA and the liver enzyme elevations is not clear. In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg, or 80 mg and 40 mg on Days 1 and 15, respectively, followed by 40 mg every other week) in patients with Crohn’s disease with control period duration ranging from 4 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 0.9% of HUMIRA-treated patients and 0.9% of control-treated patients. In controlled Phase 3 trials of HUMIRA (initial dose of 80 mg then 40 mg every other week) in patients with plaque psoriasis with control period duration ranging from 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 1.8% of HUMIRA-treated patients and 1.8% of control-treated patients.

6.6 Immuneogenicity

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 scheduled for every other week dosing, the antibody response rate was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of HUMIRA is unknown.

In patients with juvenile idiopathic arthritis, adalimumab antibodies were identified in 16% of HUMIRA-treated patients. In patients receiving concomitant methotrexate, the incidence was 6% compared to 26% with HUMIRA monotherapy.

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 3%. In patients with plaque psoriasis, the rate of antibody development with HUMIRA monotherapy was 8%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 μg/ml. Among the patients whose serum adalimumab levels were < 2 μg/ml (approximately 40% of total patients studied), the immunogenicity rate was 20.7%. In plaque psoriasis patients who were on HUMIRA monotherapy and subsequently withdrawn from the treatment, the rate of antibodies to adalimumab after retreatment was similar to the rate observed prior to withdrawal.

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. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, 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.

6.7 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. 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

<table>
<thead>
<tr>
<th>Adverse Reaction (Preferred Term)</th>
<th>HUMIRA 40 mg subcutaneous Every Other Week (N=705)</th>
<th>Placebo (N=690)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>17%</td>
<td>13%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>11%</td>
<td>9%</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>Laboratory Tests*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory test abnormal</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>Hematuria</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Alkaline phosphatase increased</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>12%</td>
<td>8%</td>
</tr>
<tr>
<td>Rash</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td>Accidental injury</td>
<td>10%</td>
<td>8%</td>
</tr>
<tr>
<td>Injection site reaction**</td>
<td>8%</td>
<td>1%</td>
</tr>
<tr>
<td>Back pain</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5%</td>
<td>3%</td>
</tr>
</tbody>
</table>

* Laboratory test abnormalities were reported as adverse reactions in European trials
** Does not include injection site erythema, itching, hemorrhage, pain or swelling

### Other Adverse Reactions

Other infrequent serious adverse reactions that do not appear in the Warnings and Precautions or Adverse Reaction sections that occurred at an incidence of less than 5% in HUMIRA-treated patients in RA studies were:

- **Body As A Whole:** Pain in extremity, pelvic pain, surgery, thorax pain
- **Cardiovascular System:** Arrhythmia, atrial fibrillation, chest pain, coronary artery disorder, heart arrest, hypertensive encephalopathy, myocardial infarct, palpitation, pericardial effusion, pericarditis, syncope, tachycardia
- **Digestive System:** Cholecystitis, cholelithiasis, esophagitis, gastroenteritis, gastrointestinal hemorrhage, hepatic necrosis, vomiting
- **Endocrine System:** Parathyroid disorder
- **Hemic And Lymphatic System:** Agranulocytosis, polycythemia
- **Musculo-Skeletal System:** Arthritis, bone disorder, bone fracture (not spontaneous), bone necrosis, joint disorder, muscle cramps, myasthenia, pyogenic arthritis, synovitis, tendon disorder
- **Neoplasia:** Adenoma
- **Nervous System:** Confusion, paresthesia, subdural hematoma, tremor
- **Respiratory System:** Asthma, bronchospasm, dyspnea, lung function decreased, pleural effusion
- **Special Senses:** Cataract
- **Thrombosis:** Thrombosis leg
- **Urogenital System:** Cystitis, kidney calculus, menstrual disorder

### Juvenile Idiopathic Arthritis Clinical Studies

In general, the adverse reactions in the HUMIRA-treated pediatric patients in the juvenile idiopathic arthritis (JIA) trial were similar in frequency and type to those seen in adult patients [see Warnings and Precautions (5), Adverse Reactions (6)]. Important findings and differences from adults are discussed in the following paragraphs.

HUMIRA was studied in 171 pediatric patients, 4 to 17 years of age, with polyarticular JIA. Severe adverse reactions reported in the study included nephritis, streptococcal pharyngitis, increased aminotransferases, herpes zoster, myositis, mitrocardia, appendicitis. Serious infections were observed in 4% of patients within approximately 2 years of initiation of treatment with HUMIRA and included cases of herpes simplex, pneumonia, urinary tract infection, pharyngitis, and herpes zoster.

A total of 45% of children experienced an infection while receiving HUMIRA with or without concomitant MTX in the first 16 weeks of treatment. The types of infections reported in HUMIRA-treated patients were generally similar to those commonly seen in JIA patients who are not treated with TNF blockers. Upon initiation of treatment, the most common adverse reactions occurring in the pediatric population treated with HUMIRA were injection site pain and injection site reaction (19% and 16%, respectively). A less commonly reported adverse event in children receiving HUMIRA was granuloma annulare which did not lead to discontinuation of HUMIRA treatment.

In the first 48 weeks of treatment, non-serious hypersensitivity reactions were seen in approximately 6% of children and included primarily localized allergic hypersensitivity reactions and allergic rash.

Isolated mild to moderate elevations of liver aminotransferases (ALT more common than AST) were observed in children with JIA exposed to HUMIRA alone; liver enzyme test elevations were more frequent among those treated with the combination of HUMIRA and MTX than those treated with HUMIRA alone. In general, these elevations did not lead to discontinuation of HUMIRA treatment.

In the JIA trial, 10% of patients treated with HUMIRA who had negative baseline anti-dsDNA antibodies developed positive titers after 48 weeks of treatment. No patient developed clinical signs of autoimmunity during the clinical trial.

Approximately 15% of children treated with HUMIRA developed mild-to-moderate elevations of creatine phosphokinase (CPK). Elevations exceeding 5 times the upper limit of normal were observed in several patients. CPK levels decreased or returned to normal in all patients. Most patients were able to continue HUMIRA without interruption.

### Psoriatic Arthritis and Ankylosing Spondylitis Clinical Studies

HUMIRA has been studied in 395 patients with psoriatic arthritis (PsA) in two placebo-controlled trials and in an open label study and in 393 patients with ankylosing spondylitis (AS) in two placebo-controlled studies. The safety profile for patients with PsA and AS treated with HUMIRA 40 mg every other week was similar to the safety profile seen in patients with RA, HUMIRA Studies RA-I through IV.

### 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 RA.

### 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 RA 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%).

### 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.

Gastrointestinal disorders: Diverticulitis, large bowel perforations including perforations associated with diverticulitis and appendiceal perforations associated with appendicitis, pancreatitis

Respiratory disorders: Interstitial lung disease, including pulmonary fibrosis

Skin reactions: Stevens Johnson Syndrome, cutaneous vasculitis, erythema multiforme, new or worsening psoriasis (all sub-types including pustular and palmoplantar)

Vascular disorders: Systemic vasculitis
7 DRUG INTERACTIONS

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

7.2 Biologic Products
In clinical studies in patients with RA, an increased risk of serious infections has been seen with the combination of TNF blockers with anakinra or abatacept, with no added benefit; therefore, use of HUMIRA with abatacept or anakinra is not recommended in patients with RA [see Warnings and Precautions (5.7 and 5.11)]. A higher rate of serious infections has also been observed in patients with RA treated with rituximab who received subsequent treatment with a TNF blocker. There is insufficient information to provide recommendations regarding the concomitant use of HUMIRA and other biologic products for the treatment of RA, PsA, AS, Crohn’s Disease, and plaque psoriasis.

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

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 efficacy of HUMIRA in pediatric patients for uses other than juvenile idiopathic arthritis (JIA) have not been established.

Juvenile Idiopathic Arthritis
In the JIA trial, HUMIRA was shown to reduce signs and symptoms of active polyarticular JIA in patients 4 to 17 years of age [see Clinical Studies (14.2)]. HUMIRA has not been studied in children less than 4 years of age, and there are limited data on HUMIRA treatment in children with weight <15 kg.

The safety of HUMIRA in pediatric patients in the JIA trial was generally similar to that observed in adults with certain exceptions [see Adverse Reactions (6.1)].

Post-marketing cases of malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers including HUMIRA [see Warnings and Precautions (5.2)].

8.5 Geriatric Use
A total of 519 rheumatoid arthritis patients 65 years of age and older, including 107 patients 75 years of age 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 65 years of age was higher than for those under 65 years of age. 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 OVERDOSE
Doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdose, 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 IgG1k 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 prefilled 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, 0.104 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.

Each pediatric prefilled syringe delivers 0.4 mL (20 mg) of drug product. Each 0.4 mL of HUMIRA contains 20 mg adalimumab, 2.47 mg sodium chloride, 0.34 mg monobasic sodium phosphate dihydrate, 0.61 mg dibasic sodium phosphate dihydrate, 0.12 mg sodium citrate, 0.052 mg citric acid monohydrate, 4.8 mg mannitol, 0.4 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, including juvenile idiopathic 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 IC50 of 1-2 X 10^9 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 (Cmax) and the time to reach the maximum concentration (Tmax) 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 (Vd) 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 µg 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.

In subjects with juvenile idiopathic arthritis (4 to 17 years of age), the mean steady-state trough serum adalimumab concentrations for subjects weighing <30 kg receiving 20 mg HUMIRA subcutaneously every other week as monotherapy or with concomitant methotrexate were 6.8 µg/mL and 10.9 µg/mL, respectively. The mean steady-state trough serum adalimumab concentrations for subjects weighing ≥30 kg receiving 40 mg HUMIRA subcutaneously every other week as monotherapy or with concomitant methotrexate were 6.6 µg/mL and 8.1 µg/mL, respectively.

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 ≥18 years of age 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-naïve 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)

<table>
<thead>
<tr>
<th>Study RA-II Monotherapy (26 weeks)</th>
<th>Study RA-III Methotrexate Combination (24 and 52 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response</strong></td>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td><strong>N=110</strong></td>
<td><strong>N=113</strong></td>
</tr>
<tr>
<td>ACR20</td>
<td></td>
</tr>
<tr>
<td>Month 6</td>
<td>19%</td>
</tr>
<tr>
<td>Month 12</td>
<td>NA</td>
</tr>
<tr>
<td>ACR50</td>
<td></td>
</tr>
<tr>
<td>Month 6</td>
<td>8%</td>
</tr>
<tr>
<td>Month 12</td>
<td>NA</td>
</tr>
<tr>
<td>ACR70</td>
<td></td>
</tr>
<tr>
<td>Month 6</td>
<td>2%</td>
</tr>
<tr>
<td>Month 12</td>
<td>NA</td>
</tr>
</tbody>
</table>

* 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 (EOW) 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

<table>
<thead>
<tr>
<th>Parameter (median)</th>
<th>Study RA-II</th>
<th>Study RA-III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
<td><strong>HUMIRA</strong></td>
<td><strong>Placebo/MTX</strong></td>
</tr>
<tr>
<td>N=110</td>
<td>N=113</td>
<td>N=200</td>
</tr>
<tr>
<td><strong>Number of tender joints (0-66)</strong></td>
<td>35</td>
<td>26</td>
</tr>
<tr>
<td><strong>Number of swollen joints (0-66)</strong></td>
<td>19</td>
<td>16</td>
</tr>
</tbody>
</table>

(continued)
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-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, 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**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo/MTX</th>
<th>HUMIRA/MTX 40 mg every other week</th>
<th>Placebo/MTX</th>
<th>HUMIRA/MTX</th>
<th>P-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Sharp score</td>
<td>2.7</td>
<td>0.1</td>
<td>2.6</td>
<td>1.4, 3.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Erosion score</td>
<td>1.6</td>
<td>0.0</td>
<td>1.6</td>
<td>0.9, 2.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>JSN score</td>
<td>1.0</td>
<td>0.1</td>
<td>0.9</td>
<td>0.3, 1.4</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*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**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MTX</th>
<th>HUMIRA/MTX 40 mg every other week</th>
<th>Placebo/MTX</th>
<th>HUMIRA/MTX</th>
<th>P-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Sharp score</td>
<td>5.7</td>
<td>4.2, 7.3</td>
<td>3.0</td>
<td>1.7, 4.3</td>
<td>0.5 (0.2,1.1)</td>
</tr>
<tr>
<td>Erosion score</td>
<td>3.7</td>
<td>2.7, 4.8</td>
<td>1.7</td>
<td>1.0, 2.4</td>
<td>0.0 (0.4,1.2)</td>
</tr>
<tr>
<td>JSN score</td>
<td>2.0</td>
<td>1.2, 2.8</td>
<td>1.3</td>
<td>0.5, 2.1</td>
<td>0.0 (0.1,0.0)</td>
</tr>
</tbody>
</table>

*95% confidence interval

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-outscome 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. Thirty-three percent of HUMIRA-treated patients achieved a 0.5 or greater improvement in HAQ-DI at a change 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 Juvenile Idiopathic Arthritis

The safety and efficacy of HUMIRA were 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 adults patients with moderately to severely active psoriatic arthritis who had suboptimal response to MTX therapy as manifested by clinical ACR responses at Week 24 and at Week 48 when all patients were on open-label HUMIRA. A modified Total Sharp Score (mTSS), which included distal interphalangeal joint involvement, 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 7. ACR Response in Study PsA-I (Percent of Patients)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>HUMIRA*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 24</td>
<td>49%</td>
<td>68%</td>
</tr>
<tr>
<td>Week 48</td>
<td>58%</td>
<td>76%</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Parameter: median</th>
<th>Placebo</th>
<th>HUMIRA*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of tender joints</td>
<td>17.0</td>
<td>24.0</td>
</tr>
<tr>
<td>Number of swollen joints</td>
<td>9.0</td>
<td>11.0</td>
</tr>
<tr>
<td>Physician global assessment</td>
<td>49.0</td>
<td>55.0</td>
</tr>
<tr>
<td>Patient global assessment</td>
<td>49.0</td>
<td>48.0</td>
</tr>
<tr>
<td>Pain</td>
<td>49.0</td>
<td>54.0</td>
</tr>
<tr>
<td>Disability index (HAQ)</td>
<td>0.9</td>
<td>1.0</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>0.7</td>
<td>0.8</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>HUMIRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 24</td>
<td>22.3</td>
<td>23.4</td>
</tr>
<tr>
<td>Week 48</td>
<td>23.4</td>
<td>23.4</td>
</tr>
</tbody>
</table>

* p<0.001 for the difference between HUMIRA and Placebo.

Physical Function Response

In Study PsA-I, physical function and disability were assessed using the HAQ Disability Index (HAQ-DI) and the SF-36 Physical 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.
14.4 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 ≥45, (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

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=107</th>
<th>HUMIRA N=208</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASAS 20 Response Criteria*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient’s Global Assessment of Disease Activity**</td>
<td>65 (60)</td>
<td>63 (38)</td>
</tr>
<tr>
<td>Total back pain*</td>
<td>67 (58)</td>
<td>65 (37)</td>
</tr>
<tr>
<td>Inflammation**</td>
<td>6.7 (6.7)</td>
<td>6.7 (3.6)</td>
</tr>
<tr>
<td>BASFI*</td>
<td>56 (51)</td>
<td>52 (34)</td>
</tr>
<tr>
<td>BASDAI§ score*</td>
<td>6.3 (5.5)</td>
<td>6.3 (3.7)</td>
</tr>
<tr>
<td>BASMI* score*</td>
<td>4.2 (4.1)</td>
<td>3.8 (3.3)</td>
</tr>
<tr>
<td>Tragus to wall (cm)</td>
<td>15.9</td>
<td>15.8</td>
</tr>
<tr>
<td>Lumbar flexion (cm)</td>
<td>4.1</td>
<td>4.0</td>
</tr>
<tr>
<td>Cervical rotation (degrees)</td>
<td>42.2</td>
<td>48.4</td>
</tr>
<tr>
<td>Lumbar side flexion (cm)</td>
<td>8.9</td>
<td>9.0</td>
</tr>
<tr>
<td>Intermalleolar distance (cm)</td>
<td>92.9</td>
<td>93.5</td>
</tr>
<tr>
<td>CRP*</td>
<td>2.2</td>
<td>2.0</td>
</tr>
</tbody>
</table>

* 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”
** mean of questions 5 and 6 of BASDAI (defined in ‘d’)
§ Bath Ankylosing Spondylitis Functional Index
§§ Bath Ankylosing Spondylitis Disease Activity Index
§§§ Bath Ankylosing Spondylitis Metrology Index
§§§§ 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.

14.5 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) ≥220 and ≤ 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 naive 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 ≥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 naive (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)

<table>
<thead>
<tr>
<th>Study</th>
<th>CD-I Placebo N=170</th>
<th>HUMIRA 160/80 mg N=176</th>
<th>CD-II Placebo N=166</th>
<th>HUMIRA 160/80 mg N=159</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>12%</td>
<td>36%**</td>
<td>7%</td>
<td>21%*</td>
</tr>
<tr>
<td>Clinical response</td>
<td>34%</td>
<td>58%**</td>
<td>34%</td>
<td>52%**</td>
</tr>
</tbody>
</table>

Clinical remission is CDAI score < 150; clinical response is decrease in CDAI of at least 70 points.

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)

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo N=172</th>
<th>40 mg HUMIRA every other week N=172</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 26</td>
<td>Clinical remission 17%</td>
<td>40%*</td>
</tr>
<tr>
<td>Clinical response</td>
<td>28%</td>
<td>54%*</td>
</tr>
<tr>
<td>Week 56</td>
<td>Clinical remission 12%</td>
<td>36%*</td>
</tr>
<tr>
<td>Clinical response</td>
<td>18%</td>
<td>43%*</td>
</tr>
</tbody>
</table>

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.

14.6 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 by 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 were not in response by Week 12, therapy continued beyond 12 weeks did not result in significantly more responses.

A total of 347 stable responders participated in a withdrawal and retreatment evaluation in an open-label extension study. Median time to relapse (decline to PGA “moderate” or worse) was approximately 5 months. During the withdrawal period, no subject experienced transformation to either pustular or erythrodermic psoriasis. A total of 178 subjects who relapsed re-initiated treatment with 80 mg of HUMIRA, then 40 mg every beginning at week 1. At week 16, 69% (123/178) of subjects had a response of PGA “clear” or “minimal.”

15 REFERENCES


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 4 alcohol preps and 4 dose trays (Psoriasis 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 0074-4339-07.

- **Pediatric Prefilled Syringe Carton - 20 mg**
  HUMIRA is supplied for pediatric use only 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 20 mg (0.4 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. Do not use if frozen even if it has been thawed. When traveling, HUMIRA should be stored in a cool carrier with an ice pack. 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 (Medication Guide). Patients or their caregivers should be provided the HUMIRA “Medication Guide” and provided an opportunity to read it and ask questions prior to initiation of therapy. The healthcare provider should ask the patient questions to determine any risk factors for treatment. Patients developing signs and symptoms of infection should seek medical evaluation immediately.

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 refilled.

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

- **Malignancies**
  Patients should be counseled about the risk of 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

Advertise patients to report any signs of new or worsening medical conditions such as congestive heart failure, neurological disease, autoimmunity disorders, or cytopenias. 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 Instructions for Use].

The following instructions refer to the use of the HUMIRA Pen:

It is important to emphasize to the patient that he/she will hear a loud ‘click’ when the plum-colored activator button is pressed. The loud click means the start of the injection. The patient must keep holding the HUMIRA Pen against the squeezed, raised skin until all of the medicine is injected. This can take up to 10 seconds. The patient will know that the injection has finished when the yellow marker fully appears in the window view and stops moving.

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.

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Revised March, 2011

Abbott Laboratories
North Chicago, IL 60064, U.S.A.

MEDICATION GUIDE

HUMIRA® (Hu-MARE-ah) (adalimumab) injection

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.

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 people taking HUMIRA. These serious infections include tuberculosis (TB) and infections caused by viruses, fungi or bacteria that have spread throughout the body. Some people have died from these infections.

• Your doctor should test you for TB before starting HUMIRA.
• Your doctor should check you closely for signs and symptoms of TB during treatment with HUMIRA.

You should not start taking HUMIRA if you have any kind of infection unless your doctor says it is okay.

Before starting HUMIRA, tell your doctor if you:

• think you have an infection or have symptoms of infection such as:
  • fever, sweats, or chills
  • muscle aches
  • cough
  • shortness of breath
  • blood in phlegm
  • weight loss
  • warm, red, or painful skin or sores on your body
  • diarrhea or stomach pain
  • burning when you urinate or urinate more often than normal
  • feel very tired

• are being treated for an infection
• get a lot of infections or have infections that keep coming back
• have diabetes
• have TB, or have been in close contact with someone with TB
• 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.
• live or have lived in certain parts of the country (such as the Ohio and Mississippi River valleys) where there is an increased risk for getting certain kinds of fungal infections (histoplasmosis, coccidiodomycosis, or blastomycosis). These infections may happen or become more severe if you use HUMIRA. Ask your doctor if you do not know if you have lived in an area where these infections are common.

• have or have had hepatitis B
• use the medicine ORENCIA® (abatacept), KINERET® (anakinra), RITUXAN® (rituximab), IMURAN® (azathioprine), or PURINETHOL® (mercaptopurine, 6-MP).
• are scheduled to have major surgery

After starting HUMIRA, call your doctor right away if you have an infection, or any sign of an infection.

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

Cancer

• For children and adults taking TNF-blockers, including HUMIRA, the chances of getting cancer may increase.
• There have been cases of unusual cancers in children, teenagers, and young adults using TNF-blockers.
• People with RA, especially more serious RA, may have a higher chance for getting a kind of cancer called lymphoma.
• If you use TNF blockers including HUMIRA your chance of getting two types of skin cancer may increase (basal cell cancer and squamous cell cancer of the skin). These types of cancer are generally not life-threatening if treated. Tell your doctor if you have a bump or open sore that doesn’t heal.
• Some people receiving TNF blockers including HUMIRA developed a rare type of cancer called hepatosplenic T-cell lymphoma. This type of cancer often results in death. Most of these people were male teenagers or young men. Also, most people were being treated for Crohn’s disease or ulcerative colitis with another medicine called IMURAN® (azathioprine) or PURINETHOL® (6-mercaptopurine).

See the “What are the possible side effects of HUMIRA?” section.

What is HUMIRA?

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

• Reduce the signs and symptoms of:
• moderate to severe rheumatoid arthritis (RA) in adults. HUMIRA can be used alone, with methotrexate, or with certain other medicines.
• moderate to severe polyarticular juvenile idiopathic arthritis (JIA) in children 4 years and older. HUMIRA can be used alone, with methotrexate, or with certain other medicines.
• psoriatic arthritis (PsA) in adults. HUMIRA can be used alone or with certain other medicines.
• ankylosing spondylitis (AS) in adults.
• moderate to severe Crohn's disease (CD) in adults when other treatments have not worked well enough.
• 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).

What should I tell my doctor before taking HUMIRA?

HUMIRA may not be right for you. 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 or have had cancer.
• have any numbness or tingling or have a disease that affects your nervous system such as multiple sclerosis or Guillain-Barré syndrome.
• have or had heart failure.
• have recently received or are scheduled to receive a vaccine. You may receive vaccines, except for live vaccines while using HUMIRA. Children with juvenile idiopathic arthritis should be brought up to date with all vaccines before starting HUMIRA.
• are allergic to rubber or latex. The needle cover on the prefilled syringe contains dry natural rubber. Tell your 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.
• are pregnant or planning to become pregnant. It is not known if HUMIRA will harm your unborn baby. HUMIRA should only be used during a pregnancy if needed. 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.
• breastfeeding or plan to breastfeed. You and your doctor should decide if you will breastfeed or use HUMIRA. You should not do both.

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 use:
• ORENCIA® (abatacept), KINERET® (anakinra), REMICADE® (infliximab), ENBREL® (etanercept), CIMZIA® (certolizumab pegol) or SIMPONI® (golimumab), because you should not use HUMIRA while you are also taking one of these medicines.
• RITUXAN® (rituximab). Your doctor may not want to give you HUMIRA if you have received RITUXAN® (rituximab) recently.
• IMURAN® (azathioprine) or PURINETHOL® (mercaptopurine, 6-MP).

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?

• 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 you were prescribed.
• See the Patient Instructions for Use inside the carton for complete instructions for the right way to prepare and inject HUMIRA.
• Make sure you have been shown how to inject HUMIRA before you do it yourself. You can call your doctor or 1-800-4HUMIRA (1-800-448-6472) if you have any questions about giving yourself an injection. Someone you know can also help you with your injection after he/she has been shown how to prepare and inject HUMIRA.
• Do not try to inject HUMIRA yourself until you have been shown the right way to give the injections. If your doctor decides that you or a caregiver may be able to give your injections of HUMIRA at home, you should receive training on the right way to prepare and inject HUMIRA.
• Do not miss any doses of HUMIRA unless your doctor says it is okay. 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. In case you are not sure when to inject HUMIRA, call your doctor or pharmacist.
• If you take more HUMIRA than you were told to take, call your doctor.

What are the possible side effects of HUMIRA?

HUMIRA can cause serious side effects, including:
See “What is the most important information I should know about HUMIRA?”
• Serious Infections.
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. People 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)
• Hepatitis B infection in people who carry the virus in their blood.
If you are a carrier of the hepatitis B virus (a virus that affects the liver), the virus can become active while you use HUMIRA. Your doctor may do blood tests before you start treatment with HUMIRA and while you are using HUMIRA. Tell your doctor if you have any of the following symptoms of a possible hepatitis B infection:
• muscle aches
• feel very tired
• dark urine
• skin or eyes look yellow
• little or no appetite
• vomiting

Allergic reactions. Allergic reactions can happen in people who use HUMIRA. Call your doctor or get medical help right away if you have any of these symptoms of a serious allergic reaction:
• hives
• swelling of your face, eyes, lips or mouth
• trouble breathing

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. Call your doctor right away if you get new worsening symptoms of heart failure while taking HUMIRA, including:
• shortness of breath
• swelling of your ankles or feet
• 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 improve when you stop HUMIRA.

Liver Problems. Liver problems can happen in people who use TNF-blocker medicines. These problems can lead to liver failure and death. Call your doctor right away if you have any of these symptoms:
• feel very tired
• skin or eyes look yellow
• poor appetite or vomiting
• pain on the right side of your stomach (abdomen)

Psoriasis. Some people using HUMIRA had new psoriasis or worsening of psoriasis they already had. Tell your doctor if you develop red scaly patches or raised bumps that are filled with pus. Your doctor may decide to stop your treatment with HUMIRA.

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 (1-800-448-6472).

What are the ingredients in HUMIRA?
Active ingredient: adalimumab

Inactive ingredients: sodium chloride, monobasic sodium phosphate dihydrate, dibasic sodium phosphate dihydrate, sodium citrate, citric acid monohydrate, mannitol, polysorbate 80, and Water for Injection. Sodium hydroxide is added as necessary to adjust pH.

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Abbott Laboratories
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Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

How should I store HUMIRA?
• Store HUMIRA in a refrigerator at 36ºF to 46ºF (2ºC to 8ºC) in the original container until it is used. Protect from light.
• When traveling, HUMIRA should be stored in a cool carrier with an ice pack.
• Do not freeze HUMIRA. Do not use HUMIRA if frozen, even if it has been thawed.
• Refrigerated HUMIRA may be used until the expiration date printed on the HUMIRA carton, dose tray, Pen or prefilled syringe.
• Do not use a Pen or prefilled syringe if the liquid is cloudy, discolored, or has flakes or particles in it.
• 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.

Common side effects with HUMIRA include:
• injection site reactions: redness, rash, swelling, itching, or bruising. These symptoms usually will go away within a few days. Call your doctor right away if you have pain, redness or swelling around the injection site that does not go away within a few days or gets worse.
• 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.