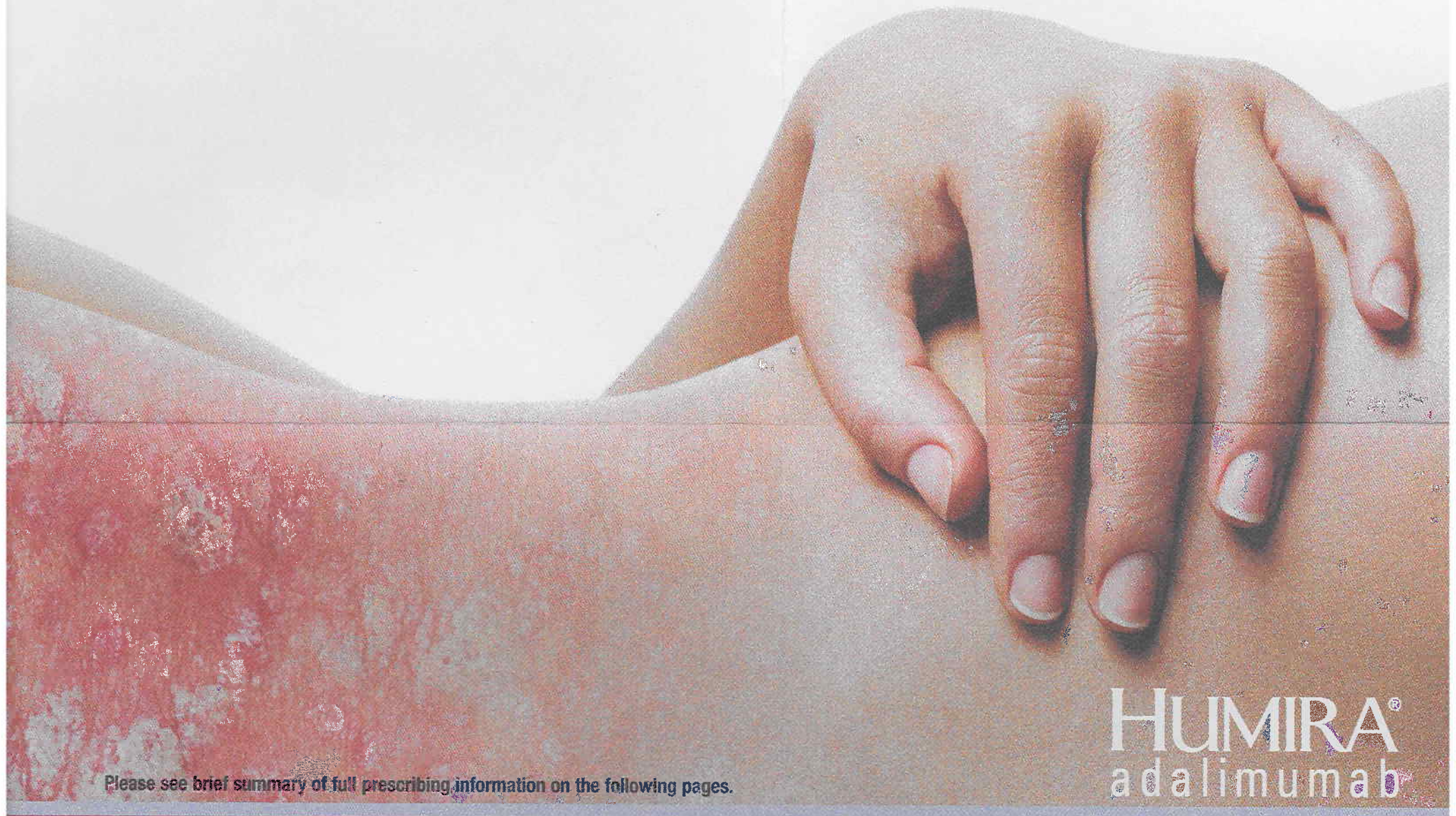
# Now approved

## for moderate to severe chronic plaque psoriasis



HUMIRA®
adalimumab

Please see brief summary of full prescribing information on the following pages.

**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** is indicated for reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage and improving physical function in patients with psoriatic arthritis. **HUMIRA** is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis. **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, and reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab. **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.

## IMPORTANT SAFETY INFORMATION

**Tuberculosis (TB), invasive fungal infections, and other opportunistic infections, have been observed in patients receiving HUMIRA. Some infections have been fatal. Anti-TB treatment of patients with latent TB infection reduces the risk of reactivation in patients receiving HUMIRA. However, active TB has developed in patients receiving HUMIRA whose screening for latent TB infection was negative. Patients should be evaluated for TB risk factors and be tested for latent TB prior to initiating HUMIRA and during therapy. When TB skin testing is performed, an induration size of 5mm or greater should be considered positive, even if vaccinated previously with Bacille Calmette-Guerin (BCG). Treatment of latent TB should be initiated prior to therapy with HUMIRA. Physicians should monitor patients receiving HUMIRA for signs and symptoms of active TB, including patients who tested negative for latent TB.**

Serious infections and sepsis, including fatalities, have been reported with the use of TNF-blocking agents, including HUMIRA. Many of these infections occurred in patients predisposed to infections because of concomitant immunosuppressive therapy in addition to their underlying disease. Patients who develop a new infection while using HUMIRA should be monitored closely. Treatment should be discontinued if a patient develops a serious infection. Do not start HUMIRA in patients with active infection (including chronic or localized). Exercise caution in patients with a history of recurrent infection or with underlying conditions, which may predispose patients to infections, or patients who have resided in regions where TB and histoplasmosis are endemic.

More cases of malignancies have been observed among patients receiving TNF blockers, including HUMIRA, compared to control patients in clinical trials. These malignancies, other than lymphoma and non-melanoma skin cancer, were similar in type and number to what would be expected in the general population. In the controlled and open-label portions of HUMIRA clinical trials, there was an approximately 3 fold higher rate of lymphoma than expected in the general population. The potential role of TNF-blocking therapy in the development of malignancies is not known. Anaphylaxis and angioneurotic edema have been reported rarely following HUMIRA administration.

Use of TNF-blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B (HBV) in patients who are chronic carriers. Some cases have been fatal. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF blocker therapy. For patients identified as carriers of HBV, exercise caution when prescribing HUMIRA, with careful evaluation and monitoring prior to and during treatment. HUMIRA should be stopped and antiviral therapy should be initiated in patients who develop hepatitis B reactivation. TNF-blocking agents, including HUMIRA, have been associated in rare cases with new onset or exacerbation of demyelinating disease. Exercise caution when considering HUMIRA for patients with these disorders.

Rare reports of pancytopenia including aplastic anemia have been reported with TNF-blocking agents. Medically significant cytopenia (e.g. thrombocytopenia, leukopenia) has been infrequently reported with HUMIRA. The causal relationship of these reports to HUMIRA remains unclear. Worsening congestive heart failure (CHF) has been observed with TNF-blocking agents, including HUMIRA, and new onset CHF has been reported with TNF-blocking agents. Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in development of a lupus-like syndrome. Discontinue treatment if symptoms of lupus-like syndrome develop. Serious infections were seen in studies with concurrent use of anakinra and another TNF-blocking agent, therefore, the combination of HUMIRA and anakinra is not recommended. Patients on HUMIRA should not receive live vaccines.

Most frequent adverse events vs placebo from rheumatoid arthritis placebo-controlled studies were injection site reactions (20% vs 14%), upper respiratory infection (17% vs 13%), injection site pain (12% vs 12%), headache (12% vs 8%), rash (12% vs 6%), and sinusitis (11% vs 9%). Discontinuations due to adverse events were 7% for HUMIRA vs 4% for placebo.

In HUMIRA clinical trials for ankylosing spondylitis, psoriatic arthritis, Crohn's disease and plaque psoriasis the safety profile for patients treated with HUMIRA was similar to the safety profile seen in patients with rheumatoid arthritis. In the placebo-controlled clinical trials in plaque psoriasis, the incidence of arthralgia was 3% in HUMIRA-treated patients versus 1% in controls.



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PROFESSIONAL BRIEF SUMMARY
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# HUMIRA®
(adalimumab)

**WARNING: RISK OF SERIOUS INFECTIONS**

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

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

## INDICATIONS AND USAGE

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

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

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

**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.

**Plaque Psoriasis**
HUMIRA is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. HUMIRA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician *[see Boxed WARNINGS and Warnings and Precautions]*.

## CONTRAINDICATIONS

None.

## WARNINGS AND PRECAUTIONS

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

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

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

Before initiation of therapy with HUMIRA, patients should be evaluated for tuberculosis risk factors and should be tested for latent tuberculosis infection. Treatment of latent tuberculosis infections should be initiated prior to therapy with HUMIRA.

All patients treated with HUMIRA should have a thorough history taken prior to initiating therapy. Some patients who have previously received treatment for latent or active tuberculosis have developed active tuberculosis while being treated with TNF blocking agents. Anti-tuberculosis therapy should be considered prior to initiation of HUMIRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Anti-tuberculosis therapy prior to initiating HUMIRA should also be considered in patients who have several, or highly significant, risk factors for tuberculosis infection and have a negative test for latent tuberculosis, but the decision to initiate anti-tuberculosis therapy in these patients should only be made after taking into account both the risk for latent tuberculosis infection and the risks of anti-tuberculosis therapy.

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

**Malignancies**
In the controlled portions of clinical trials of some TNF-blocking agents, including HUMIRA, more cases of malignancies have been observed among patients receiving those TNF blockers compared to control patients. During the controlled portions of HUMIRA trials in patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and plaque psoriasis, malignancies, other than lymphoma and non-melanoma (basal cell and squamous cell) skin cancer, were observed at a rate (95% confidence interval) of 0.6 (0.3, 1.0)/100 patient-years among 3853 HUMIRA-treated patients versus a rate of 0.4 (0.2, 1.0)/100 patient-years among 2183 control patients (median duration of treatment of 5.5 months for HUMIRA-treated patients and 3.9 months for control-treated patients). The size of the control group and limited duration of the controlled portions of studies precludes the ability to draw firm conclusions. In the controlled and uncontrolled open-label portions of the clinical trials of HUMIRA, the more frequently observed malignancies, other than lymphoma and non-melanoma skin cancer, were breast, colon, prostate, lung, and melanoma. These malignancies in HUMIRA-treated and control-treated patients were similar in type and number to what would be expected in the general population. During the controlled portions of HUMIRA rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and plaque psoriasis trials, the rate (95% confidence interval) of non-melanoma (basal cell and squamous cell) skin cancers was 0.9 (0.57, 1.35)/100 patient-years among HUMIRA-treated patients and 0.3 (0.08, 0.80)/100 patient-years among control patients. The potential role of TNF blocking therapy in the development of malignancies is not known.

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

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

**Hepatitis B Virus Reactivation**
Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF blocker therapy. Prescribers should exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. 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.

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

**Hematological Reactions**
Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., thrombocytopenia, leukopenia) have been infrequently reported with HUMIRA *[see Adverse Reactions]*. 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.

**Use with Anakinra**
Serious infections were seen in clinical studies with concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocking agent, with no added benefit. Therefore, the combination of HUMIRA and anakinra is not recommended *[see Drug Interactions]*.

**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. Physicians should exercise caution when using HUMIRA in patients who have heart failure and monitor them carefully.

**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]*.

**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. 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.

**Immunosuppression**
The possibility exists for TNF blocking agents, including HUMIRA, to affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. The safety and efficacy of HUMIRA in patients with immunosuppression have not been evaluated.

## ADVERSE REACTIONS

**Clinical Studies Experience**
The most serious adverse reactions were *[see Warnings and Precautions]*:

- Serious Infections
- Neurologic Reactions
- Malignancies

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

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

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

*Tuberculosis and Opportunistic Infections*
In completed and ongoing global clinical studies that include over 13,000 patients, the overall rate of tuberculosis is approximately 0.26 per 100 patient-years. In over 4500 patients in the US and Canada, the

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

*Malignancies*

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

*Autoantibodies*

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

*Immunogenicity*

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

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

*Other Adverse Reactions*

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

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

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

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

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

*Psoriatic Arthritis and Ankylosing Spondylitis Clinical Studies*

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

*Crohn's Disease Clinical Studies*

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

*Plaque Psoriasis Clinical Studies*

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

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

**Postmarketing Experience**

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

*Hematologic reactions:* Thrombocytopenia *[see Warnings and Precautions]*

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

*Respiratory disorders:* Interstitial lung disease, including pulmonary fibrosis

*Skin reactions:* Cutaneous vasculitis, erythema multiforme

## DRUG INTERACTIONS

**Anakinra**

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

**Live Vaccines**

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

**Methotrexate**

Although methotrexate reduces the apparent adalimumab clearance, the data does not suggest the need for dose adjustment of either HUMIRA or methotrexate.

## USE IN SPECIFIC POPULATIONS

**Pregnancy**

Pregnancy Category B - There are 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.

**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.

**Pediatric Use**

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

**Geriatric Use**

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

## OVERDOSAGE

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

## PATIENT COUNSELING INFORMATION

**Patient Counseling**

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

- **Immunosuppression**
  Inform patients that HUMIRA may lower the ability of their immune system to fight infections. Instruct the patient of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis and reactivation of hepatitis B virus infections.
- **Allergic Reactions**
  Patients should be advised to seek immediate medical attention if they experience any symptoms of severe allergic reactions. Advise latex-sensitive patients that the needle cap of the prefilled syringe contains latex.
- **Other Medical Conditions**
  Advise patients to report any signs of new or worsening medical conditions such as heart disease, neurological disease, or autoimmune disorders. Advise patients to report any symptoms suggestive of a cytopenia such as bruising, bleeding, or persistent fever.

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