

PRODUCT MONOGRAPH

Pr HUMIRA[®]
adalimumab

40 mg in 0.8 mL sterile solution (50 mg/mL) subcutaneous injection

Biological Response Modifier

HUMIRA[®] (adalimumab) treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, or psoriasis, and familiar with the HUMIRA[®] efficacy and safety profile.

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HUMIRA[®]

adalimumab

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Non-medicinal Ingredients
subcutaneous injection	sterile solution / 40 mg in 0.8 mL (50 mg/mL)	citric acid monohydrate, dibasic sodium phosphate dihydrate, mannitol, monobasic sodium phosphate dihydrate, polysorbate 80, sodium citrate, sodium chloride. <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

DESCRIPTION

HUMIRA[®] (adalimumab) is a recombinant human immunoglobulin (IgG1) monoclonal antibody. Adalimumab was created using phage display technology resulting in fully human heavy and light chain variable regions, which confer specificity to human tumor necrosis factor (TNF), and human IgG1 heavy chain and kappa light chain sequences. Adalimumab binds with high affinity and specificity to soluble tumor necrosis factor (TNF-alpha) but not lymphotoxin (TNF-beta). Adalimumab is produced by recombinant DNA technology in a mammalian cell expression system. It consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons.

INDICATIONS AND CLINICAL USE

HUMIRA[®] (adalimumab) treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), or psoriasis (Ps), and familiar with the HUMIRA[®] efficacy and safety profile.

HUMIRA[®] is indicated for:

Rheumatoid Arthritis

- reducing the signs and symptoms, inducing major clinical response and clinical remission, 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 (MTX) or other disease-modifying anti-rheumatic drugs (DMARDs).

When used as first-line treatment in recently diagnosed patients who have not been previously treated with methotrexate, HUMIRA[®] should be given in combination with methotrexate. HUMIRA[®] can be given as monotherapy in case of intolerance to methotrexate or when treatment with methotrexate is contraindicated.

Psoriatic Arthritis

- reducing the signs and symptoms of active arthritis and inhibiting the progression of structural damage and improving the physical function in adult psoriatic arthritis patients. HUMIRA[®] can be used in combination with methotrexate (MTX) in patients who do not respond adequately to methotrexate alone.

Ankylosing Spondylitis

- reducing signs and symptoms in patients with active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Crohn's Disease

- 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, including corticosteroids and/or immunosuppressants. 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.

Psoriasis

- treatment of adult patients with chronic moderate to severe psoriasis who are candidates for systemic therapy. For patients with chronic moderate plaque psoriasis, HUMIRA[®] should be used after phototherapy has been shown to be ineffective or inappropriate.

Geriatrics (> 65 years of age):

Evidence from clinical studies and experience suggests that use of HUMIRA[®] in the geriatric population is not associated with differences in effectiveness. A brief discussion can be found under (**WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**).

Pediatrics (< 18 years of age):

Safety and effectiveness in pediatric patients have not been fully established.

CONTRAINDICATIONS

- Patients with known hypersensitivity to HUMIRA[®] (adalimumab) or any of its components. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.
- Patients with severe infections such as sepsis, tuberculosis and opportunistic infections. See (**WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions, Infections**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Hepatosplenic T-Cell Lymphoma

Very rare post-marketing reports of hepatosplenic T-cell lymphoma (HSTCL), a rare aggressive lymphoma that is often fatal, have been identified in patients treated with HUMIRA[®] (adalimumab). Most of the patients had prior infliximab therapy as well as concomitant azathioprine or 6-mercaptopurine use for Crohn's disease. The causal association of HSTCL with HUMIRA[®] is not clear.

Infections

Serious infections due to bacterial, mycobacterial, invasive fungal (disseminated or extrapulmonary histoplasmosis, aspergillosis, coccidioidomycosis), viral, parasitic, or other opportunistic infections have been reported in patients receiving tumor necrosis factor (TNF)-blocking agents. Sepsis, rare cases of tuberculosis, candidiasis, listeriosis, and pneumocystis have also been reported with the use of TNF-blocking agents, including HUMIRA[®]. Other serious infections seen in clinical trials include pneumonia, pyelonephritis, septic arthritis and septicemia. Hospitalization or fatal outcomes associated with infections have been reported. Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their underlying disease, could predispose them to infections.

Treatment with HUMIRA[®] should not be initiated in patients with active infections, including chronic or localized infections, until infections are controlled. In patients who have been exposed to tuberculosis, and patients who have traveled in areas of high risk of tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis, the risk and benefits of treatment with HUMIRA[®] should be considered prior to initiating therapy. See

(WARNINGS AND PRECAUTIONS, Infections, Other Opportunistic Infections).

As with other TNF-blockers, patients should be monitored closely for infections (including tuberculosis) before, during and after treatment with HUMIRA®.

Patients who develop a new infection while undergoing treatment with HUMIRA® should be monitored closely and undergo a complete diagnostic evaluation. Administration of HUMIRA® should be discontinued if a patient develops a serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated.

Physicians should exercise caution when considering the use of HUMIRA® in patients with a history of recurrent infection or with underlying conditions which may predispose them to infections, or patients who have resided in regions where tuberculosis and histoplasmosis are endemic. See **(WARNINGS AND PRECAUTIONS, Infections, Tuberculosis)** and **(ADVERSE REACTIONS, Adverse Drug Reaction Overview, Infections)**. The benefits and risks of treatment with HUMIRA® should be carefully considered before initiating therapy.

Pediatric Malignancy

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF-blockers, including HUMIRA®. See **(WARNINGS AND PRECAUTIONS, Malignancies)**.

General

Use with Anakinra

Serious infections were seen in clinical studies with concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocking agent, etanercept, with no added benefit compared to etanercept alone. Because of the nature of the adverse events seen with the combination of etanercept and anakinra, similar toxicities may also result from the combination of anakinra and other TNF-blocking agents. Therefore, the combination of HUMIRA® (adalimumab) and anakinra is not recommended. See **(DRUG INTERACTIONS, Drug-Drug Interactions)**.

Switching Between Biological DMARDs

When switching from one biologic to another, patients should continue to be monitored for signs of infection.

Carcinogenesis and Mutagenesis

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

assay, respectively. See (**TOXICOLOGY, Mutagenicity and Carcinogenicity, In vitro Genotoxicity**).

Cardiovascular

Patients with Congestive Heart Failure

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

Gastrointestinal

Small Bowel Obstruction

Failure to respond to treatment for Crohn's disease may indicate the presence of fixed fibrotic stricture that may require surgical treatment. Available data suggest that HUMIRA[®] does not worsen or cause strictures.

Hematologic Events

Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF-blocking agents. Adverse events 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 (e.g., persistent fever, bruising, bleeding, pallor) while on HUMIRA[®]. Discontinuation of HUMIRA[®] therapy should be considered in patients with confirmed significant hematologic abnormalities.

Hypersensitivity Reactions

Allergic reactions (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed in approximately 1% of patients receiving HUMIRA[®] in clinical trials. See (**ADVERSE REACTIONS**). Serious allergic reactions, including anaphylaxis, have been reported very rarely following post-marketing HUMIRA[®] administration. If an anaphylactic reaction or other serious allergic reactions occur, administration of HUMIRA[®] should be discontinued immediately and appropriate therapy initiated.

The needle cover of the syringe contains dry natural rubber (latex). This may cause severe allergic reactions in patients sensitive to this substance. See (**DOSAGE AND ADMINISTRATION, Administration, Pen or Pre-filled Syringe**).

Immune

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, Adverse Drug Reaction Overview, Autoantibodies**).

Immunosuppression

The possibility exists for TNF-blocking agents, including HUMIRA[®], to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 64 patients with rheumatoid arthritis who were treated with HUMIRA[®], there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector T- and B-cells and NK-cells, monocyte/macrophages, and neutrophils. The impact of treatment with HUMIRA[®] on the development and course of malignancies, as well as active and/or chronic infections, is not fully understood. See (**WARNINGS AND PRECAUTIONS, Infections and Malignancies**) and (**ADVERSE REACTIONS, Adverse Drug Reaction Overview, Infections and Malignancies**).

Immunizations

In a randomized, double-blind, placebo-controlled study in 226 adult rheumatoid arthritis patients treated with HUMIRA[®], antibody responses to concomitant pneumococcal and influenza vaccines were assessed. Protective antibody levels to the pneumococcal antigens were achieved by 86% of patients in the HUMIRA[®] group compared to 82% in the placebo group. A total of 37% of HUMIRA[®]-treated subjects and 40% of placebo-treated subjects achieved at least a 2-fold increase in antibody titer to at least three out of five pneumococcal antigens. In the same study, 98% of patients in the HUMIRA[®] group and 95% in the placebo group achieved protective antibody levels to the influenza antigens. A total of 52% of HUMIRA[®]-treated subjects and 63% of placebo-treated subjects achieved at least a 4-fold increase in antibody titer to at least two out of three influenza antigens.

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[®].

Infections

Tuberculosis

As observed with other TNF-blocking agents, tuberculosis (frequently disseminated or extrapulmonary at clinical presentation) associated with the administration of HUMIRA[®] in clinical trials has been reported. See (**WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions, Infections**). 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, during and after treatment with HUMIRA[®], patients should be evaluated for active or latent tuberculosis infection with a tuberculin skin test. Treatment of latent tuberculosis infections should be initiated prior to therapy with HUMIRA[®]. When tuberculin skin testing is performed for latent tuberculosis infection, an induration size of 5 mm or greater should be considered positive, even if vaccinated previously with Bacille Calmette-Guérin (BCG).

The possibility of undetected latent tuberculosis should be considered especially in patients who have immigrated from or traveled to countries with a high prevalence of tuberculosis or who had close contact with a person with active tuberculosis. If latent infection is diagnosed, appropriate prophylaxis in accordance with the Canadian Tuberculosis Standards and Centers for Disease Control and Prevention guidelines should be instituted. Anti-tuberculosis therapy prior to initiating HUMIRA[®] should also be considered in patients who have a negative test for latent tuberculosis but have risk factors for tuberculosis infection. The decision to initiate anti-tuberculosis therapy in these patients should only be made after taking into account both the risk for latent tuberculosis infection and the risks of anti-tuberculosis therapy. If necessary, consultation should occur with a physician with expertise in the treatment of tuberculosis. Active tuberculosis has developed in patients receiving HUMIRA[®] whose screening for latent tuberculosis infection was negative, and some patients who have previously received treatment for latent or active tuberculosis have developed active tuberculosis while being treated with TNF-blocking agents.

Patients receiving HUMIRA[®] should be monitored for signs and symptoms of active tuberculosis, particularly because tests for latent tuberculosis infection may be falsely negative. The risk of false negative tuberculin skin test results should be considered especially in patients who are severely ill or immunocompromised. Patients should be instructed to seek medical advice if signs/symptoms (e.g., persistent cough, wasting/weight loss, low grade fever) suggestive of a tuberculosis infection occur, and physicians should monitor for signs and symptoms of active tuberculosis, including patients who are tuberculosis skin test negative.

Other Opportunistic Infections

Opportunistic infections, including invasive fungal infections, have been observed in patients receiving HUMIRA[®]. These infections are not consistently recognized in patients taking TNF-blockers and this has resulted in delays in appropriate treatment, sometimes resulting in fatal outcomes.

Patients taking TNF-blockers are more susceptible to serious fungal infections such as histoplasmosis, coccidioidomycosis, blastomycosis, aspergillosis, candidiasis, and other opportunistic infections. Those who develop fever, malaise, weight loss, sweats, cough, dyspnea, and/or pulmonary infiltrates, or other serious systemic illness with or without concomitant shock should promptly seek medical attention for a diagnostic evaluation.

For patients who reside or travel in regions where mycoses are endemic, invasive fungal infections should be suspected if they develop the signs and symptoms of possible systemic fungal infection. Patients are at risk of histoplasmosis and other invasive fungal infections and hence clinicians should consider empiric antifungal treatment until the pathogen(s) are identified. 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. Patients who develop a severe fungal infection are also advised to stop the TNF-blocker until infections are controlled.

Hepatitis B Virus (HBV) Reactivation

Very rare cases of hepatitis B virus (HBV) reactivation have been associated with anti-TNF therapy. Clinically active HBV infection occurred following a latency period ranging from 3 to 20 months after initiation of therapy. In the majority of cases, patients were also taking other immunosuppressive drugs, including methotrexate, azathioprine, and/or corticosteroids. Hence, establishing a causal relationship to anti-TNF agents is confounded by the presence of these other medications. Where outcome information was provided, most patients were reported to have improved after antiviral treatment and/or discontinuation of the anti-TNF agent. However, fatal outcomes have also occurred in reported cases. Patients at risk of HBV infection should be evaluated for prior evidence of HBV infection before initiating anti-TNF therapy. Those identified as chronic carriers (i.e., surface antigen positive) should be monitored for signs and symptoms of active HBV infection throughout the course of therapy and for several months following discontinuation of therapy. Reactivation of HBV is not unique to anti-TNF-alpha agents and has been reported with other immunosuppressive drugs.

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.

In the controlled and uncontrolled open-label portions of clinical trials of HUMIRA[®], the more frequently observed malignancies, other than lymphoma and non-melanoma skin cancer, were breast, colon, prostate, lung, and melanoma.

Malignancies, some fatal, have been reported among children and adolescents who received treatment with TNF-blocking agents. 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. The malignancies occurred after a median of 30 months of therapy. 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 post-marketing reports.

Cases of acute and chronic leukemia have been reported in association with post-marketing TNF-blocker use in rheumatoid arthritis and other indications. Patients with rheumatoid arthritis may be at a higher risk (up to 2-fold) than the general population for the development of leukemia, even in the absence of TNF-blocking therapy.

Lymphoma

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.

However, for HUMIRA[®], the occurrence of lymphoma was rare, and the follow-up period of placebo patients was shorter than for patients receiving TNF-antagonist therapy. The size of the control group and limited duration of the controlled portions of studies precludes the ability to draw firm conclusions. Furthermore, there is an increased background lymphoma risk in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates the risk estimation.

In combining the controlled and uncontrolled open-label portions of these clinical trials with a median duration of approximately 1.7 years, including 6539 patients and over 16,000 patient-years of therapy, the observed rate of lymphomas is approximately 0.11 per 100 patient-years. This is approximately 3-fold higher than expected in the general population.

During the long-term open-label trials with HUMIRA[®], the overall standard incidence ratio (SIR) of malignancies was 0.99 [95% confidence interval (CI), 0.81 – 1.20]. With current knowledge in this area, a possible risk for development of lymphomas or other malignancies in patients treated with a TNF-antagonist cannot be excluded.

No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving HUMIRA[®]. Additional caution should be exercised when considering HUMIRA[®] treatment in these patients.

Non-Lymphoma Malignancy

During the controlled portions of HUMIRA[®] trials in patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and psoriasis, malignancies, other than lymphoma and non-melanoma skin cancer, were observed at a rate (95% CI) of 6.6 (4.0, 10.8) per 1000 patient-years among 3917 HUMIRA[®]-treated patients versus a rate of 4.2 (1.8, 10.1) per 1000 patient-years among 2247 control patients (median duration of treatment of 5.6 months for HUMIRA[®]-treated patients and 4.0 months for control-treated patients).

During the controlled portions of HUMIRA[®] rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and psoriasis trials, the rate (95% CI) of non-melanoma skin cancers was 9.9 (6.6, 14.8) per 1000 patient-years among HUMIRA[®]-treated patients and 2.5 (0.8, 7.9) per 1000 patient-years among control patients. Of these skin cancers, squamous cell carcinomas occurred at rates (95% CI) of 2.5 (1.1, 5.5) per 1000 patient-years among

HUMIRA[®]-treated patients and 0.8 (0.1, 6.0) per 1000 patient-years among control patients. The rate (95% CI) of lymphomas was 0.8 (0.2, 3.3) per 1000 patient-years among HUMIRA[®]-treated patients and 0.8 (0.1, 6.0) per 1000 patient-years among control patients.

The observed rate of malignancies, other than lymphoma and non-melanoma skin cancers, is approximately 9.1 per 1000 patient years in the controlled portion of clinical trials and in ongoing and completed open-label extension studies. The observed rate of non-melanoma skin cancers is approximately 10.1 per 1000 patient years, and the observed rate of lymphomas is approximately 1.1 per 1000 patient years. The median duration of these studies is approximately 3.4 years and included 4,954 patients who were on HUMIRA[®] for at least one year or who developed a malignancy within a year of starting therapy, representing over 21,021 patient years of therapy.

All patients, and in particular psoriasis patients with a medical history of extensive immunosuppressant therapy or psoriasis patients with a history of Psoralen Ultra-Violet A (PUVA) treatment should be examined for the presence of non-melanoma skin cancer prior to and during treatment with HUMIRA[®].

Neurologic Events

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, including multiple sclerosis. Prescribers should exercise caution in considering the use of HUMIRA[®] in patients with preexisting or recent onset central nervous system demyelinating disorders.

Special Populations

Pregnant Women

The extent of exposure in pregnancy during clinical trials is very limited, consisting only of individual cases.

An embryo-fetal perinatal developmental toxicity study has been performed in *cynomolgus* monkeys at dosages up to 100 mg/kg (266 times human area under the curve (AUC) when given 40 mg adalimumab subcutaneously with methotrexate every week, or 373 times when given 40 mg adalimumab 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.

Labor and Delivery

There are no known effects of HUMIRA[®] on labor or delivery.

Nursing Women

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 adalimumab, 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.

Pediatrics (< 18 years of age)

Safety and effectiveness in pediatric patients have not been fully established.

Geriatrics (> 65 years of age)

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 to RA IV. No overall differences in effectiveness were 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 the age of 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.

Monitoring and Laboratory Tests

There is no known interference between HUMIRA[®] and laboratory tests.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most serious adverse reactions were [see (**WARNINGS AND PRECAUTIONS**)]:

- serious infections
- neurologic events
- malignancies

The most common adverse reaction in rheumatoid arthritis patients treated with HUMIRA[®] (adalimumab) was injection site reactions. In controlled trials for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and psoriasis, 15% of patients treated with HUMIRA[®] developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 9% of patients receiving control treatment. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

The proportion of rheumatoid arthritis patients who discontinued treatment due to adverse events during the double-blind, placebo-controlled portion of rheumatoid arthritis Studies RA I, RA II,

RA III, and RA IV was 7.0% for patients taking HUMIRA[®], and 4.0% for placebo-treated patients. The most common adverse events leading to discontinuation of HUMIRA[®] were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%).

Among patients with rheumatoid arthritis in placebo-controlled studies, deaths occurred in 8 of 1380 (0.58%) HUMIRA[®]-treated patients compared to 1 of 690 (0.14%) placebo-treated patients. The rate of deaths in both treatment arms is less than expected in the normal population with a standard mortality ratio (SMR) of 0.87 (95% CI, 0.38, 1.72) in the HUMIRA[®] group and 0.25 (95% CI, 0.00, 1.37) in the placebo group.

HUMIRA[®] has also been studied in 542 patients with early rheumatoid arthritis (disease duration less than three years) who were methotrexate naïve (Study RA V). No new safety signals were seen in this patient population compared to the safety profile seen in HUMIRA[®] Studies RA I to RA IV. In this study, deaths occurred in 5 of 542 (0.92%) HUMIRA[®]-treated patients compared to 1 of 257 (0.39%) methotrexate-treated patients. The rate of deaths in both treatment arms is less than expected in the normal population with a standard mortality ratio (SMR) of 0.57 (95% CI, 0.18, 1.32) in the HUMIRA[®] group and 0.22 (95% CI, 0.00, 1.23) in the methotrexate group.

HUMIRA[®] has also been studied in 395 patients with psoriatic arthritis in two placebo-controlled studies and in an open-label extension study, in 393 patients with ankylosing spondylitis in two placebo-controlled studies and in over 1500 patients with Crohn's disease in five placebo-controlled and two open-label extension studies. The safety profile for patients with psoriatic arthritis treated with HUMIRA[®] 40 mg every other week was similar to the safety profile seen in patients with rheumatoid arthritis, HUMIRA[®] Studies RA I to RA V. During the controlled period of the psoriatic arthritis studies, no deaths occurred in the HUMIRA[®]-treated or placebo-treated patients. During the psoriatic arthritis open-label study, two deaths occurred in 382 patients with 795.7 patient-years of exposure. The rate of deaths is less than expected in the normal population with a standard mortality ratio (SMR) of 0.39 (95% CI, 0.04, 1.43). Among patients enrolled in the psoriasis open-label study, 5 deaths occurred in 1,468 patients with 4,068.6 patient-years of exposure.

Autoantibodies

Patients had serum samples tested for autoantibodies at multiple time points in Studies RA I to RA V. In those rheumatoid arthritis controlled trials, 11.9% of patients treated with HUMIRA[®] and 8.1% of placebo- or active control-treated patients who had negative baseline antinuclear antibody (ANA) titers, developed positive titers at Week 24. Two patients out of 3441 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

Formation of anti-adalimumab antibodies is associated with increased clearance and reduced efficacy of HUMIRA[®]. There is no apparent correlation between the presence of anti-adalimumab antibodies and adverse events.

Rheumatoid arthritis 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% (58/1062) 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%). 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 American College of Rheumatology (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 psoriatic arthritis, anti-adalimumab antibodies were identified in 38/376 subjects (10%) treated with HUMIRA[®]. In patients not given concomitant methotrexate, the incidence was 13.5% (24/178 subjects), compared to 7% (14/198 subjects) when HUMIRA[®] was used as add-on to methotrexate.

In patients with ankylosing spondylitis, anti-adalimumab antibodies were identified in 17/204 subjects (8.3%) treated with HUMIRA[®]. In patients not given concomitant methotrexate, the incidence was 16/185 (8.6%), compared to 1/19 (5.3%) when HUMIRA[®] was used as add-on to methotrexate.

In patients with Crohn's disease, anti-adalimumab antibodies were identified in 2.6% (7/269) of patients receiving HUMIRA[®].

In patients with psoriasis, anti-adalimumab antibodies were identified in 77/920 subjects (8.4%) treated with HUMIRA[®] monotherapy.

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 mcg/mL. Among these patients whose serum adalimumab levels were < 2 mcg/mL (approximately 40% of total patients studied), the immunogenicity rate was 20.7%. In patients with plaque psoriasis on long term HUMIRA[®] monotherapy who participated in a withdrawal and retreatment study and whose serum adalimumab levels were < 2 mcg/mL (approximately 12% of total patients studied), the immunogenicity rate was 16%; the overall rate of antibody development prior to withdrawal was 1.9%, and 2.3% after retreatment.

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

Infections

In controlled trials for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and psoriasis, the rate of infection was 1.50 per patient-year in the HUMIRA[®]-treated patients and 1.42 per patient-year in the control-treated patients. The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, and sinusitis. Most patients continued on HUMIRA[®] after the infection resolved.

The incidence of serious infections was 0.03 per patient-year in HUMIRA[®]-treated patients and 0.03 per patient-year in placebo and active control-treated patients.

In controlled and open-label studies with HUMIRA[®], serious infections (including fatal infections, which occurred rarely) have been reported, which include reports of tuberculosis (including miliary and extra-pulmonary locations) and invasive opportunistic infections (e.g., disseminated histoplasmosis, pneumocystis carinii pneumonia, aspergillosis and listeriosis). Most of the cases of tuberculosis occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease.

Injection Site Reactions

In controlled trials, 15% of patients treated with HUMIRA[®] developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 9% of patients receiving placebo or active control. Injection site reactions generally did not necessitate discontinuation of the medicinal product.

Malignancies

More cases of malignancy have been observed in HUMIRA[®]-treated patients compared to control-treated patients in clinical trials. See (**WARNINGS AND PRECAUTIONS, Malignancies**).

Psoriasis: New Onset and Worsening

Cases of new onset psoriasis, including pustular psoriasis and palmoplantar psoriasis, and cases of worsening of pre-existing psoriasis have been reported with the use of TNF-blockers, including HUMIRA[®]. Many of these patients were taking concomitant immunosuppressants (e.g., methotrexate, corticosteroids). Some of these patients required hospitalization. Most patients had improvement of their psoriasis following discontinuation of their TNF-blocker. Some patients have had recurrences of the psoriasis when they were re-challenged with a

different TNF-blocker. Discontinuation of HUMIRA[®] should be considered for severe cases and those that do not improve or that worsen despite topical treatments.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Rheumatoid Arthritis

Description of Data Sources

The data described below reflect exposure to HUMIRA[®] in 3046 patients, including more than 2000 patients exposed for six months, and more than 1500 exposed for more than one year (Studies RA I, RA II, RA III, RA IV, and RA V). HUMIRA[®] was studied in placebo-controlled trials and in long-term follow-up studies for up to 60 months duration in patients with moderately to severely active rheumatoid arthritis who had failed previous DMARD therapy; the mean age was 54 years, 77% were female and 91% Caucasian (Studies RA I, RA II, RA III, RA IV). A further study (Study RA V) was in patients with recently diagnosed rheumatoid arthritis who had not previously been treated with methotrexate. Most patients received HUMIRA[®] 40 mg every other week.

Relative Frequency of Adverse Drug Reactions

Table 1 summarizes adverse drug reactions reported at a rate of at least 1% in patients treated with HUMIRA[®] 40 mg every other week, as well as all doses of HUMIRA[®] tested, compared to placebo or methotrexate (Study RA V). Adverse reaction rates in patients treated with HUMIRA[®] 40 mg weekly were similar to rates in patients treated with HUMIRA[®] every other week. In Study RA III, the types and frequencies of adverse drug reactions in the 5-year open-label extension were similar to those observed in the one-year double-blind portion.

Table 1. Number and Percentage of Subjects with $\geq 1\%$ Treatment-Emergent Adverse Events at Least Possibly Related to Study Drug During the Control Period in Rheumatoid Arthritis Studies (Studies RA I, RA II, RA III, RA IV, RA V)

System Organ Class (SOC)	HUMIRA® 40 mg s.c. eow N = 1247 n (%)	HUMIRA® (all adalimumab) N = 1922 n (%)	Placebo (not Study RA V) N = 690 n (%)	MTX (Study RA V) N = 257 n (%)
Gastrointestinal Disorders				
Nausea	80 (6.4)	112 (5.8)	12 (1.7)	33 (12.8)
Diarrhea	47 (3.8)	60 (3.1)	17 (2.5)	18 (7.0)
Abdominal pain	22 (1.8)	29 (1.5)	5 (0.7)	3 (1.2)
Abdominal pain upper	20 (1.6)	25 (1.3)	0 (0.0)	13 (5.1)
Mouth ulceration	17 (1.4)	24 (1.2)	5 (0.7)	12 (4.7)
Dyspepsia	14 (1.1)	21 (1.1)	4 (0.6)	7 (2.7)
Vomiting	16 (1.3)	20 (1.0)	5 (0.7)	6 (2.3)
General Disorders and Administration Site Conditions				
Injection site irritation	74 (5.9)	122 (6.3)	61 (8.8)	3 (1.2)
Injection site reaction	49 (3.9)	67 (3.5)	3 (0.4)	2 (0.8)
Injection site pain	36 (2.9)	63 (3.3)	24 (3.5)	6 (2.3)
Injection site erythema	36 (2.9)	60 (3.1)	2 (0.3)	1 (0.4)
Fatigue	37 (3.0)	58 (3.0)	7 (1.0)	9 (3.5)
Injection site rash	17 (1.4)	22 (1.1)	2 (0.3)	0 (0.0)
Influenza-like illness	15 (1.2)	21 (1.1)	2 (0.3)	8 (3.1)
Pyrexia	13 (1.0)	20 (1.0)	1 (0.1)	6 (2.3)
Infections and Infestations				
Nasopharyngitis	61 (4.9)	95 (4.9)	10 (1.5)	28 (10.9)
Upper respiratory infection	72 (5.8)	93 (4.8)	15 (2.2)	17 (6.6)
Sinusitis	46 (3.7)	55 (2.9)	17 (2.5)	4 (1.6)
Herpes simplex	33 (2.6)	48 (2.5)	6 (0.9)	5 (1.9)
Urinary tract infection	31 (2.5)	44 (2.3)	6 (0.9)	7 (2.7)
Bronchitis	19 (1.5)	29 (1.5)	8 (1.2)	9 (3.5)
Herpes zoster	17 (1.4)	23 (1.2)	8 (1.2)	2 (0.8)
Influenza	16 (1.3)	21 (1.1)	7 (1.0)	5 (1.9)
Pneumonia	17 (1.4)	21 (1.1)	3 (0.4)	1 (0.4)
Investigations				
Lymphocyte count decreased	11 (0.9)	38 (2.0)	11 (1.6)	1 (0.4)
Alanine aminotransferase increased	27 (2.2)	33 (1.7)	4 (0.6)	9 (3.5)
Liver function test abnormal	19 (1.5)	22 (1.1)	4 (0.6)	7 (2.7)

System Organ Class (SOC)	HUMIRA[®] 40 mg s.c. eow N = 1247 n (%)	HUMIRA[®] (all adalimumab) N = 1922 n (%)	Placebo (not Study RA V) N = 690 n (%)	MTX (Study RA V) N = 257 n (%)
Musculoskeletal and Connective Tissue Disorders				
Rheumatoid arthritis	11 (0.9)	28 (1.5)	7 (1.0)	2 (0.8)
Nervous System Disorders				
Headache	75 (6.0)	124 (6.5)	14 (2.0)	14 (5.4)
Dizziness	23 (1.8)	32 (1.7)	6 (0.9)	3 (1.2)
Respiratory, Thoracic and Mediastinal Disorders				
Pharyngolaryngeal pain	33 (2.6)	44 (2.3)	9 (1.3)	7 (2.7)
Cough	31 (2.5)	42 (2.2)	4 (0.6)	9 (3.5)
Skin and Subcutaneous Tissue Disorders				
Rash	44 (3.5)	66 (3.4)	9 (1.3)	8 (3.1)
Pruritus	28 (2.2)	43 (2.2)	4 (0.6)	5 (1.9)
Alopecia	22 (1.8)	28 (1.5)	2 (0.3)	6 (2.3)
Rash pruritic	14 (1.1)	22 (1.1)	0 (0.0)	3 (1.2)

Definition(s): s.c. = subcutaneous ; eow = every other week

Psoriatic Arthritis

Table 2 summarizes adverse drug reactions reported in placebo-controlled and open-label studies at a rate of at least 1% in psoriatic arthritis patients treated with HUMIRA[®] 40 mg every other week.

Table 2. Number and Percentage of Subjects with \geq 1% Treatment-Emergent Adverse Events at Least Possibly Related to Study Drug During the Control and Open-Label Periods in Psoriatic Arthritis Studies (Studies PsA I, PsA II, and PsA III)

System Organ Class (SOC)	Double-Blind Study		Open-Label Study
	Placebo N = 211 n (%)	HUMIRA[®] 40 mg s.c. eow N = 202 n (%)	HUMIRA[®] 40 mg s.c. eow N = 382 n (%)
Gastrointestinal Disorders			
Nausea	2 (0.9)	2 (1.0)	3 (0.8)
General Disorders and Administration Site Conditions			
Injection site reaction	5 (2.4)	11 (5.4)	21 (5.5)
Injection site pain	8 (3.8)	8 (4.0)	2 (0.5)
Injection site erythema	0 (0.0)	4 (2.0)	2 (0.5)
Injection site burning	4 (1.9)	4 (2.0)	4 (1.0)

System Organ Class (SOC)	Double-Blind Study		Open-Label Study
	Placebo N = 211 n (%)	HUMIRA [®] 40 mg s.c. eow N = 202 n (%)	HUMIRA [®] 40 mg s.c. eow N = 382 n (%)
Fatigue	5 (2.4)	0 (0.0)	4 (1.0)
Infections and Infestations			
Upper respiratory infection	7 (3.3)	8 (4.0)	17 (4.5)
Herpes simplex	3 (1.4)	6 (3.0)	7 (1.8)
Skin fungal infection NOS	0 (0.0)	3 (1.5)	-
Pharyngitis	1 (0.5)	2 (1.0)	4 (1.0)
Sinusitis	4 (1.9)	2 (1.0)	12 (3.1)
Urinary tract infection	0 (0.0)	2 (1.0)	6 (1.6)
Bronchitis	1 (0.5)	1 (0.5)	5 (1.3)
Nasopharyngitis	2 (0.9)	1 (0.5)	8 (2.1)
Influenza	2 (0.9)	0 (0.0)	5 (1.3)
Investigations			
Liver function tests abnormal	1 (0.5)	2 (1.0)	5 (1.3)
Nervous System Disorders			
Headache	5 (2.4)	5 (2.5)	5 (1.3)
Paresthesia	1 (0.5)	3 (1.5)	2 (0.5)
Respiratory, Thoracic, and Mediastinal Disorders			
Rhinitis NOS	0 (0.0)	3 (1.5)	3 (0.8)
Skin and Subcutaneous Tissue Disorders			
Erythema	0 (0.0)	3 (1.5)	-

Definition(s): s.c. = subcutaneous; eow = every other week

Ankylosing Spondylitis

HUMIRA[®] has been studied in 393 patients with ankylosing spondylitis in two placebo-controlled studies. The safety profile for patients with 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 to RA IV. **Table 3** summarizes adverse drug reactions reported at a rate of at least 1% in ankylosing spondylitis patients treated with HUMIRA[®] 40 mg every other week compared to placebo.

Table 3. Number and Percentage of Subjects with $\geq 1\%$ Treatment-Emergent Adverse Events at Least Possibly Related to Study Drug During the Control Period in Ankylosing Spondylitis Studies (Studies AS I and AS II)

System Organ Class (SOC)	HUMIRA [®] 40 mg s.c. eow N = 246 n (%)	Placebo N = 151 n (%)
General Disorders and Administration Site Conditions		
Fatigue	5 (2.0)	3 (2.0)
Injection site erythema	5 (2.0)	1 (0.7)
Injection site irritation	4 (1.6)	2 (1.3)
Injection site pain	6 (2.4)	3 (2.0)
Injection site reaction	8 (3.3)	1 (0.7)
Infections and Infestations		
Nasopharyngitis	8 (3.3)	0 (0.0)
Upper respiratory tract infection	5 (2.0)	2 (1.3)
Nervous System Disorders		
Dizziness	3 (1.2)	3 (2.0)
Headache	11 (4.5)	4 (2.6)
Skin and Subcutaneous Tissue Disorders		
Eczema	3 (1.2)	1 (0.7)
Pruritus	4 (1.6)	1 (0.7)
Pruritus generalized	3 (1.2)	0 (0.0)
Rash	4 (1.6)	1 (0.7)
Urticaria	3 (1.2)	0 (0.0)

Definition(s): s.c. = subcutaneous; eow = every other week

Crohn's Disease

HUMIRA[®] has been studied in over 1500 patients with Crohn's disease in five 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 including the safety profile for patients in placebo-controlled Study CD VI. No new safety signals occurred during the open-label long-term studies with HUMIRA[®] exposure up to 5 years. The safety profile of HUMIRA[®] in Crohn's disease remains unaltered.

Table 4 and

Table 5 summarize adverse drug reactions reported at a rate of at least 1% in Crohn's disease patients treated with HUMIRA[®] in induction and maintenance studies, respectively.

Table 4. Number and Percentage of Subjects with $\geq 1\%$ Treatment-Emergent Adverse Events at Least Possibly Related to Study Drug During Administration of Induction Study Medications in Crohn's Disease Studies (Studies CD I and CD II)

System Organ Class (SOC)	HUMIRA® 160/80 mg N = 235 n (%)	HUMIRA® 80/40 mg N = 75 n (%)	Placebo N = 240 n (%)
Eye Disorders			
Corneal pigmentation	0 (0.0)	1 (1.3)	0 (0.0)
Visual disturbance	0 (0.0)	1 (1.3)	0 (0.0)
Gastrointestinal Disorders			
Abdominal pain	5 (2.1)	0 (0.0)	2 (0.8)
Abdominal pain lower	3 (1.3)	0 (0.0)	0 (0.0)
Change of bowel habit	0 (0.0)	1 (1.3)	0 (0.0)
Cheilitis	0 (0.0)	1 (1.3)	1 (0.4)
Constipation	2 (0.9)	1 (1.3)	3 (1.3)
Crohn's disease	2 (0.9)	1 (1.3)	3 (1.3)
Flatulence	3 (1.3)	0 (0.0)	0 (0.0)
Nausea	6 (2.6)	0 (0.0)	4 (1.7)
Vomiting	1 (0.4)	1 (1.3)	3 (1.3)
General Disorders and Administration Site Conditions			
Asthenia	0 (0.0)	1 (1.3)	1 (0.4)
Chills	0 (0.0)	2 (2.7)	1 (0.4)
Fatigue	2 (0.9)	1 (1.3)	10 (4.2)
Influenza like illness	0 (0.0)	2 (2.7)	2 (0.8)
Injection site bruising	5 (2.1)	1 (1.3)	1 (0.4)
Injection site erythema	4 (1.7)	0 (0.0)	0 (0.0)
Injection site irritation	19 (8.1)	8 (10.7)	14 (5.8)
Injection site pain	6 (2.6)	4 (5.3)	9 (3.8)
Injection site pruritus	3 (1.3)	0 (0.0)	0 (0.0)
Injection site reaction	11 (4.7)	5 (6.7)	6 (2.5)
Pain	2 (0.9)	1 (1.3)	3 (1.3)
Pyrexia	3 (1.3)	3 (1.3)	3 (1.3)
Infections and Infestations			
Staphylococcal infection	0 (0.0)	1 (1.3)	0 (0.0)
Investigations			
Double stranded DNA antibody	0 (0.0)	1 (1.3)	0 (0.0)
White blood cell count increased	0 (0.0)	1 (1.3)	0 (0.0)
Metabolism and Nutrition Disorders			
Hypokalemia	0 (0.0)	1 (1.3)	0 (0.0)

System Organ Class (SOC)	HUMIRA[®] 160/80 mg N = 235 n (%)	HUMIRA[®] 80/40 mg N = 75 n (%)	Placebo N = 240 n (%)
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	3 (1.3)	1 (1.3)	2 (0.8)
Back pain	0 (0.0)	1 (1.3)	0 (0.0)
Muscle spasms	0 (0.0)	1 (1.3)	1 (0.4)
Pain in extremity	0 (0.0)	1 (1.3)	0 (0.0)
Nervous System Disorders			
Dizziness	3 (1.3)	0 (0.0)	2 (0.8)
Headache	8 (3.4)	2 (2.7)	7 (2.9)
Restless legs syndrome	0 (0.0)	1 (1.3)	0 (0.0)
Reproductive System and Breast Disorders			
Genital pruritus female	0 (0.0)	1 (1.3)	0 (0.0)
Skin and Subcutaneous Tissue Disorders			
Eczema	1 (0.4)	1 (1.3)	0 (0.0)
Erythema	1 (0.4)	1 (1.3)	1 (0.4)
Hyperhidrosis	0 (0.0)	1 (1.3)	0 (0.0)
Onychorrhexis	0 (0.0)	1 (1.3)	0 (0.0)
Pruritus	1 (0.4)	0 (0.0)	4 (1.7)
Rash	2 (0.9)	2 (2.7)	1 (0.4)
Rash maculo-papular	1 (0.4)	1 (1.3)	0 (0.0)
Rash pruritic	0 (0.0)	1 (1.3)	1 (0.4)

Table 5. Number and Percentage of Subjects with $\geq 1\%$ Treatment-Emergent Adverse Events at Least Possibly Related to Study Drug During Administration of Blinded Study Maintenance Medications in Crohn's Disease Studies (Studies CD III and CD IV)

System Organ Class (SOC)	HUMIRA[®] 40 mg s.c. eow, 40 mg ew N = 554 n (%)	Placebo N = 279 n (%)
Gastrointestinal Disorders		
Abdominal pain	7 (1.3)	4 (1.4)
Crohn's disease	9 (1.6)	9 (3.2)
Diarrhea	7 (1.3)	1 (0.4)
Nausea	9 (1.6)	5 (1.8)
General Disorders and Administration Site Conditions		
Fatigue	10 (1.8)	1 (0.4)

System Organ Class (SOC)	HUMIRA[®] 40 mg s.c. eow, 40 mg ew N = 554 n (%)	Placebo N = 279 n (%)
Injection site bruising	6 (1.1)	1 (0.4)
Injection site erythema	10 (1.8)	0 (0.0)
Injection site irritation	18 (3.2)	2 (0.7)
Injection site pain	8 (1.4)	2 (0.7)
Injection site reaction	26 (4.7)	1 (0.4)
Pyrexia	7 (1.3)	5 (1.8)
Infections and Infestations		
Herpes simplex	6 (1.1)	4 (1.4)
Nasopharyngitis	8 (1.4)	2 (0.7)
Rhinitis	7 (1.3)	1 (0.4)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	9 (1.6)	2 (0.7)
Nervous System Disorders		
Headache	19 (3.4)	6 (2.2)
Skin and Subcutaneous Tissue Disorders		
Rash	11 (2.0)	5 (1.8)
Definition(s): s.c. = subcutaneous; ew = every week; eow = every other week		

Psoriasis

HUMIRA[®] has been studied in 1696 patients with psoriasis in placebo-controlled and open-label extension studies. The safety profile for patients with psoriasis treated with HUMIRA[®] was similar to the safety profile seen in patients with rheumatoid arthritis. Safety results of the long-term open-label study are consistent with the known safety profile of HUMIRA[®] in other psoriasis studies. **Table 6** summarizes adverse drug reactions reported at a rate of at least 1% in psoriasis patients treated with an initial dose of HUMIRA[®] 80 mg followed by HUMIRA[®] 40 mg every other week compared to placebo or methotrexate.

Table 6. Number and Percentage of Subjects \geq 1% Reporting Treatment-Emergent Adverse Events Possibly or Probably Related to Study Drug in Controlled Psoriasis Studies (Studies Ps I, Ps II and Ps III)

System Organ Class (SOC)	HUMIRA [®] 80 mg x 1, then 40 mg s.c. eow N = 966 n (%)	Placebo + MTX N = 613 n (%)
Gastrointestinal Disorders		
Nausea	10 (1.0)	11 (1.8)
General Disorders and Administration Site Conditions		
Injection site reaction	29 (3.0)	9 (1.5)
Injection site irritation	16 (1.7)	6 (1.0)
Injection site pain	14 (1.5)	9 (1.5)
Fatigue	10 (1.0)	5 (0.8)
Infections and Infestations		
Upper respiratory infection	12 (1.2)	3 (0.5)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	10 (1.0)	3 (0.5)
Nervous System Disorders		
Headache	19 (2.0)	14 (2.3)

Definition(s): s.c. = subcutaneous; eow = every other week; MTX = methotrexate

Other Common Clinical Trial Adverse Drug Reactions

Other clinical trial adverse reactions occurring at an incidence of \geq 1% that were observed among the various indications include:

Eye Disorders: conjunctivitis, visual impairment

Renal and Urinary Disorders: hematuria, renal impairment

Less Common Clinical Trial Adverse Drug Reactions (< 1%)

Infrequent serious adverse drug reactions occurring at an incidence of less than 1% in patients treated with HUMIRA[®] in Studies RA I to RA V, Studies PsA I and PsA II, Studies AS I and AS II, CD Maintenance Studies, and Studies Ps I to Ps III:

Blood and Lymphatic System Disorders: agranulocytosis, anemia, eosinophilia, leukopenia, lymphadenopathy, lymphocytosis, neutropenia, pancytopenia

Cardiac Disorders: arrhythmia supraventricular, cardiac arrest, chest pain, palpitations

Eye Disorders:	blepharitis, diplopia, eye swelling
Gastrointestinal Disorders:	abdominal pain, anal fistula, Crohn's disease, frequent bowel movements, hemorrhoidal hemorrhage, pancreatitis, rectal hemorrhage, small intestine obstruction
General Disorders and Administration Site Conditions:	death, non-cardiac chest pain, pyrexia
Hepatobiliary Disorders:	hepatic necrosis
Immune System Disorders:	hypersensitivity
Infections and Infestations:	abscess, abscess limb, arthritis bacterial, bronchitis, cellulitis, cystitis, device-related infection, diverticulitis, erysipelas, escherichia sepsis, gastroenteritis, herpes virus infection, herpes zoster, histoplasmosis, infected skin ulcer, infection, lobar pneumonia, lower respiratory tract infection, meningitis viral, mycobacterium avium complex infection, necrotizing fasciitis, perianal abscess, pneumonia, pneumonia pneumococcal, pyelonephritis, respiratory tract infection, sepsis, septic shock, sinusitis, tuberculosis, urinary tract infection, urosepsis, wound infection
Injury, Poisoning and Procedural Complications:	postoperative wound complication
Investigations:	double-stranded DNA antibody, hepatic enzyme increased
Musculoskeletal and Connective Tissue Disorders:	arthritis, arthropathy, back pain, muscular weakness, musculoskeletal chest pain, osteitis, rheumatoid arthritis, systemic lupus erythematosus
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps):	basal cell carcinoma, B-cell lymphoma, breast cancer, malignant melanoma <i>in situ</i> , metastases to liver, ovarian cancer, squamous cell carcinoma, testicular seminoma (pure)
Nervous System Disorders:	clonus, hyperreflexia, hypertensive encephalopathy, intention tremor, multiple sclerosis, paresthesia, tremor
Psychiatric Disorders:	confusional state
Renal and Urinary Disorders:	nocturia
Reproductive System and Breast Disorders:	cervical dysplasia, endometrial hyperplasia
Respiratory, Thoracic and Mediastinal Disorders:	bronchospasm, lung infiltration, pleural effusion, pleurisy, pneumonitis, respiratory failure
Skin and Subcutaneous Tissue Disorders:	psoriasis, pustular psoriasis, rash

Surgical and Medical Procedures: arthrodesis

Vascular Disorders: circulatory collapse, rheumatoid vasculitis

Abnormal Hematologic and Clinical Chemistry Findings

There are no known laboratory tests that may be helpful in following the patient's response or in identifying possible adverse reactions.

In controlled rheumatoid arthritis clinical trials (Studies RA I to RA IV), elevations of alanine aminotransferase (ALT) were similar in patients receiving HUMIRA[®] or placebo. In patients with early rheumatoid arthritis (disease duration of less than three years) (Study RA V), elevations of ALT were more common in the combination arm (HUMIRA[®] + methotrexate) compared to the methotrexate monotherapy arm or the HUMIRA[®] monotherapy arm.

In psoriatic arthritis clinical trials, elevations in ALT were more common in psoriatic arthritis patients compared with patients in rheumatoid arthritis clinical studies.

In controlled Crohn's disease clinical trials, elevations of ALT were similar in patients receiving HUMIRA[®] or placebo.

In all indications, patients with raised ALT were asymptomatic and in most cases, elevations were transient and resolved on continued treatment.

Post-Market Adverse Drug Reactions

The following post-market adverse drug reactions have been reported:

Cardiac Disorders: myocardial infarction

Gastrointestinal Disorders: intestinal perforation

Hematologic Events: thrombocytopenia[†]

Hypersensitivity Reactions: anaphylaxis[‡], angioedema, angioneurotic edema

Immune System Disorders: sarcoidosis

Infections: reactivation of hepatitis B virus (HBV)[†]

Musculoskeletal and Connective Tissue Disorders: lupus-like syndrome^{†*}

Neoplasia: hepatosplenic T-cell lymphoma (HSTCL)[†], leukemia[†]

Nervous System Disorders: cerebrovascular accident, demyelinating disorders (e.g., Guillain-Barré syndrome, optic neuritis)

Skin Reactions: alopecia, cutaneous vasculitis, erythema multiforme, new onset or worsening of psoriasis (including palmoplantar pustular psoriasis)*, Stevens-Johnson syndrome

Respiratory, Thoracic and Mediastinal Disorders: interstitial lung disease (including pulmonary fibrosis), pulmonary embolism

† See (WARNINGS AND PRECAUTIONS)

* See (ADVERSE REACTIONS, Adverse Drug Reaction Overview)

DRUG INTERACTIONS

Serious Drug Interactions

- Serious infections and sepsis, including fatalities, have been reported with the use of TNF-blocking agents, including HUMIRA[®] (adalimumab). 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. Tuberculosis and invasive opportunistic fungal infections have been observed in patients treated with TNF-blocking agents, including HUMIRA[®].

Overview

Population pharmacokinetic analyses with data from over 1200 rheumatoid arthritis patients revealed that co-administration of methotrexate had an intrinsic effect on the apparent clearance of adalimumab (CL/F). See (DRUG INTERACTIONS, Drug-Drug Interactions). As expected, there was a trend toward higher apparent clearance of adalimumab with increasing body weight and in the presence of anti-adalimumab antibodies.

Other more minor factors were also identified: higher apparent clearance was predicted in rheumatoid arthritis patients receiving doses lower than the recommended dose, and in rheumatoid arthritis patients with high rheumatoid factor or C-reactive protein (CRP) concentrations. These factors are not likely to be clinically important.

HUMIRA[®] (adalimumab) has been studied in rheumatoid arthritis patients taking concomitant methotrexate. See (CLINICAL TRIALS). The data do not suggest the need for dose adjustment of either HUMIRA[®] or methotrexate.

Drug-Drug Interactions

Table 7. Established or Potential Drug-Drug Interactions

Concomitant Drug Name	Clinical Comment
Abatacept	Concurrent administration of TNF-blockers and abatacept has been associated with an increased risk of infections including serious infections compared to TNF-blockers alone. This combination has not demonstrated increased clinical benefit. Thus the combined use of TNF-blockers and abatacept is not recommended.
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, General, Use with Anakinra).
Methotrexate (MTX)	When HUMIRA [®] was administered to 21 rheumatoid arthritis patients on stable MTX therapy, there were no statistically significant changes in the serum MTX concentration profiles. In contrast, after single and multiple dosing, MTX reduced adalimumab apparent clearances by 29 and 44% respectively, in patients with rheumatoid arthritis. See (CLINICAL TRIALS).
Other	Interactions between HUMIRA [®] and drugs other than MTX have not been evaluated in formal pharmacokinetic studies. In rheumatoid arthritis clinical trials where HUMIRA [®] was co-administered with commonly-used DMARDs (sulfasalazine, hydrochloroquine, leflunomide and parenteral gold), glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs or analgesics, no safety signals were seen. There is no data on other DMARDs, and patients with prior treatment with alkylating agents (e.g., cyclophosphamide) were excluded.

Definition(s): DMARDs = disease-modifying anti-rheumatic drugs; MTX = methotrexate; TNF = tumor necrosis factor

Drug-Food Interactions

HUMIRA[®] is administered as a subcutaneous injection. Interactions with food are therefore not applicable.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

There are no known laboratory tests that may be helpful in following the patient's response or in identifying possible adverse reactions.

Drug-Lifestyle Interactions

HUMIRA[®] may have a minor influence on the ability to drive and use machines. Dizziness (including vertigo, vision disorder and fatigue) may occur following administration of HUMIRA[®].

DOSAGE AND ADMINISTRATION

Dosing Considerations

Pediatrics

Safety and effectiveness in pediatric patients have not been fully established.

Geriatrics

Evidence from clinical studies and experience suggests that use of HUMIRA[®] (adalimumab) in the geriatric population is not associated with differences in effectiveness. No dose adjustment is needed for this population. A brief discussion can be found under **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**.

Gender

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.

Race

No differences in immunoglobulin clearance would be expected among races. From limited data in non-Caucasians, no important kinetic differences were observed for adalimumab. Dosage adjustment is not required.

Hepatic Insufficiency

No pharmacokinetic data are available in patients with hepatic impairment. No dose recommendation can be made.

Renal Insufficiency

No pharmacokinetic data are available in patients with renal impairment. No dose recommendation can be made.

Disease States

Healthy volunteers and patients with rheumatoid arthritis displayed similar adalimumab pharmacokinetics. See (**ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Disease States**).

Concomitant Medications

Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics or other DMARDs may be continued during treatment with HUMIRA[®]. When treated with HUMIRA[®] as monotherapy, some rheumatoid arthritis patients who experience a decrease in their response to HUMIRA[®] 40 mg every other week, may benefit from an increase in dose intensity to HUMIRA[®] 40 mg every week.

Recommended Dose and Dosage Adjustment

Rheumatoid Arthritis

The recommended dose of HUMIRA[®] for adult patients with rheumatoid arthritis is 40 mg administered every other week as a subcutaneous injection.

Psoriatic Arthritis

The recommended dose of HUMIRA[®] for adult patients with psoriatic arthritis is 40 mg administered every other week as a subcutaneous injection.

For the rheumatoid arthritis and psoriatic arthritis indications, available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

Ankylosing Spondylitis

The recommended dose of HUMIRA[®] for patients with ankylosing spondylitis is HUMIRA[®] 40 mg administered every other week as a single-dose via subcutaneous injection. Glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs, analgesics or disease modifying anti-rheumatic drugs can be continued during treatment with HUMIRA[®].

Crohn's Disease

The recommended HUMIRA[®] induction dose regimen for adult patients with Crohn's disease is 160 mg at Week 0 (dose can be administered as four subcutaneous injections in one day or as two subcutaneous injections per day for two consecutive days), followed by 80 mg at Week 2.

The recommended HUMIRA[®] maintenance dose regimen for adult patients with Crohn's disease is 40 mg every other week beginning at Week 4.

During treatment with HUMIRA[®], other concomitant therapies (e.g., corticosteroids and/or immunomodulatory agents) should be optimized.

For patients who experience a disease flare, dose escalation may be considered.
See (**CLINICAL TRIALS**).

Some patients who have not responded by Week 4 (induction period) may benefit from continued maintenance therapy through Week 12. Available data suggest that the clinical response is usually achieved at Week 4 of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

The use of HUMIRA[®] in Crohn's disease has been evaluated up to 1 year in controlled clinical studies. In open-label studies, 510/1594 patients were evaluated for 3 years, and 118/1594 patients for at least 5 years.

Psoriasis

The recommended dose of HUMIRA[®] for adult patients with psoriasis is an initial dose of 80 mg administered subcutaneously, followed by 40 mg subcutaneously given every other week starting one week after the initial dose.

Continued therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period.

Missed Dose

Patients who miss a dose of HUMIRA[®] should be advised to inject this missed dose as soon as they become aware of it, and then follow with their next scheduled dose.

Administration

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

The solution in the Pen or pre-filled 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 in the syringe should be discarded.

NOTE: The needle cover of the syringe contains a dry natural rubber (latex), which should not be handled by persons sensitive to this substance.

Patients using the pre-filled syringes 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 **CONSUMER INFORMATION**.

Injection sites should be rotated and injections should never be given into areas where the skin is tender, bruised, red or hard. See (**CONSUMER INFORMATION**).

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

The maximum tolerated dose of HUMIRA[®] (adalimumab) has not been established in humans. Multiple 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Adalimumab binds specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also lyses surface TNF-expressing cells in vitro in the presence of complement. Adalimumab does not bind or inactivate lymphotoxin (TNF-beta). TNF is a naturally-occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis patients and play an important role in both pathologic inflammation and joint destruction that are hallmarks of these diseases. Increased levels of TNF are also found in psoriasis plaques, which contribute to the inflammatory response, to the proliferation and decreased maturation of keratinocytes and to the associated vascular damages that are characteristic of the disease.

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 a half maximal inhibitory concentration (IC₅₀) of 1 to 2 x 10⁻¹⁰M].

Pharmacodynamics

After treatment with HUMIRA[®] (adalimumab), a rapid 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 rapid 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.

The serum adalimumab concentration-efficacy relationship as measured by the American College of Rheumatology response criteria (ACR 20) appears to follow the Hill E_{\max} equation as shown in **Figure 1**.

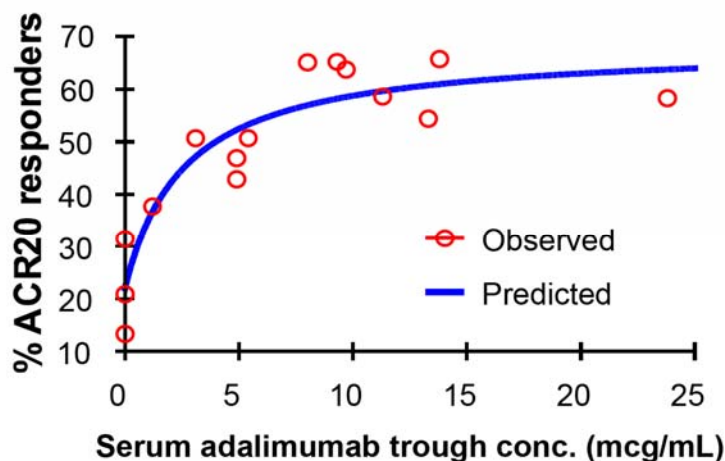


Figure 1. Serum Adalimumab Concentration-Efficacy Relationship as Measured by the American College of Rheumatology Response Criteria (ACR 20)

The half maximal effective concentration (EC_{50}) estimates ranging from 0.8 to 1.4 mcg/mL were obtained through pharmacokinetic / pharmacodynamic modelling of swollen joint count, tender joint count and ACR 20 response from patients participating in Phase 2 and 3 trials.

Pharmacokinetics

The single-dose pharmacokinetics of adalimumab in rheumatoid arthritis patients were determined in several studies with intravenous doses ranging from 0.25 to 10.0 mg/kg. The distribution volume (V_{ss}) ranged from 4.7 to 6.0 L. The systemic clearance of adalimumab is approximately 12 mL/h. The mean terminal half-life was approximately 2 weeks, ranging from 10 to 20 days across studies. The pharmacokinetics of adalimumab were linear over the dose range of 0.5 to 10.0 mg/kg following a single intravenous dose.

Adalimumab mean steady-state trough concentrations of approximately 5 mcg/mL and 8 to 9 mcg/mL, were observed in rheumatoid arthritis patients with and without methotrexate, respectively. The 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.

Population pharmacokinetic analyses in patients with rheumatoid arthritis revealed that there was a trend toward higher apparent clearance of adalimumab in the presence of anti-adalimumab antibodies.

In patients with psoriatic arthritis, adalimumab mean steady-state trough concentrations of 8.5 to 12 mcg/mL and 6 to 10 mcg/mL were observed in patients with and without methotrexate, respectively.

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 concentrations of approximately 12 mcg/mL at Week 2 and Week 4. Mean steady-state trough levels of approximately 7 mcg/mL were observed at Week 24 and Week 56 in Crohn's disease patients who received a maintenance dose of HUMIRA[®] 40 mg every other week.

Population pharmacokinetic analysis in patients with Crohn's disease revealed a lower apparent clearance of adalimumab as compared to patients with rheumatoid arthritis.

In patients with psoriasis, the mean steady-state trough concentration was 5 mcg/mL during HUMIRA[®] 40 mg every other week monotherapy treatment.

Absorption

The maximum serum concentration (C_{max}) and the time to reach the maximum concentration (T_{max}) were 4.7 ± 1.6 mcg/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.

Distribution

Adalimumab concentrations in the synovial fluid from five rheumatoid arthritis patients ranged from 31 to 96% of those in serum.

Metabolism

No formal studies have been conducted to evaluate the metabolism of adalimumab. However, as adalimumab is an IgG1 antibody of entirely human sequences, it is expected that its metabolism would follow the course of other IgG molecules.

Excretion

No formal studies have been conducted to evaluate the excretion of adalimumab. However, as adalimumab is an IgG1 antibody of entirely human sequences, it is expected that its excretion would follow the course of other IgG molecules.

Special Populations and Conditions

Pediatrics

HUMIRA[®] has not been studied in children.

Geriatrics

Population pharmacokinetic analyses in patients with rheumatoid arthritis revealed that there was a trend toward lower clearance with increasing age in patients aged 40 to > 75 years.

Gender

Population pharmacokinetic analyses in patients with rheumatoid arthritis revealed that no gender-related pharmacokinetic differences were observed after correction for a patient's body weight.

Race

No differences in immunoglobulin clearance would be expected among races. From limited data in non-Caucasians, no important kinetic differences were observed for adalimumab.

Hepatic Insufficiency

No pharmacokinetic data are available in patients with hepatic impairment.

Renal Insufficiency

No pharmacokinetic data are available in patients with renal impairment.

Disease States

Healthy volunteers and patients with rheumatoid arthritis displayed similar adalimumab pharmacokinetics. Population pharmacokinetic analyses predicted minor increases in apparent clearance in patients receiving doses lower than the recommended dose and in patients with high rheumatoid factor or C-reactive protein (CRP) concentrations. These increases are not likely to be clinically important. See (**DOSAGE AND ADMINISTRATION, Dosing Considerations, Disease States**).

STORAGE AND STABILITY

HUMIRA[®] (adalimumab) must be refrigerated between 2 and 8°C. Store in original carton until time of administration. **DO NOT FREEZE**. Protect from light. Do not use beyond the expiration date.

SPECIAL HANDLING INSTRUCTIONS

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

A healthcare professional (e.g., doctor, nurse or pharmacist) should be consulted for instructions on how to properly dispose of used needles and syringes (including the Pen). Special provincial or local laws regarding the proper disposal of needles and syringes should be followed. Needles or syringes (including the Pen) should **NEVER** be thrown in the household trash or recycling bin.

- Used needles and syringes (including the Pen) should be placed in a container made especially for this purpose (“Sharps” container), or a hard plastic container with a screw-on cap or metal container with a plastic lid labelled “Used Syringes”. Glass or clear plastic containers should not be used.
- The container should always be kept out of the reach of children.
- When the container is about two-thirds full, the cap or lid should be taped down so that it does not come off. The container should be disposed of as instructed by a healthcare professional. **CONTAINERS SHOULD NEVER BE THROWN IN THE HOUSEHOLD TRASH OR RECYCLING BIN.**
- Unless otherwise instructed by a healthcare professional, used alcohol pads may be placed in the trash. Dose trays and covers may be recycled.

DOSAGE FORMS, COMPOSITION AND PACKAGING

HUMIRA[®] (adalimumab) is supplied as a sterile solution for subcutaneous administration in the following packaging configurations:

Pen

HUMIRA[®] Pen is available in a carton containing two dose trays. Each dose tray contains one alcohol pad and a single-use Pen, containing a 1 mL pre-filled glass syringe with a fixed 27 gauge ½ inch needle, providing 40 mg adalimumab dissolved in 0.8 mL sterile solution (50 mg/mL).

Pre-Filled Syringe

HUMIRA[®] is also available in a carton containing two dose trays. Each dose tray contains one alcohol pad and a single-use, 1 mL pre-filled glass syringe with a fixed 27 gauge ½ inch needle, providing 40 mg adalimumab dissolved in 0.8 mL sterile solution (50 mg/mL).

Listing of Non-Medicinal Ingredients

In addition to the active ingredient adalimumab, each HUMIRA[®] 50 mg/mL Pen or pre-filled syringe contains the following non-medicinal ingredients: citric acid monohydrate, dibasic sodium phosphate dihydrate, mannitol, monobasic sodium phosphate dihydrate, polysorbate 80, sodium citrate, sodium chloride, sodium hydroxide (added as necessary to adjust pH), and water for injection.

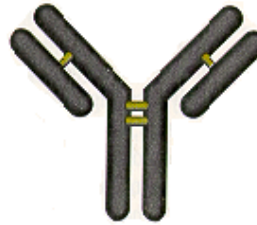
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	adalimumab
Chemical name:	Not applicable. Adalimumab is not a chemical. It is an immunoglobulin (recombinant human IgG1 monoclonal antibody).
Molecular formula and molecular mass:	Total apparent molecular weight of 148 kilodaltons (kDa), as determined by Q-TOF and SDS-PAGE analysis.

Structural formula:



Physicochemical properties:	Adalimumab is an IgG antibody composed of two kappa light chains each with a molecular weight of approximately 23 kDa and two IgG1 heavy chains each with a molecular weight of approximately 51 kDa for a total apparent molecular weight of 148 kDa, as determined by Q-TOF and SDS-PAGE analysis.
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HUMIRA[®] is supplied as a sterile, preservative-free solution for subcutaneous administration. The solution of adalimumab is clear and colorless, with a pH of 5.2.

Product characteristics:	HUMIRA [®] (adalimumab) is a recombinant human immunoglobulin (IgG1) monoclonal antibody specific for human tumor necrosis factor (TNF). Adalimumab was created using phage display technology resulting in an antibody with human derived heavy and light chain variable regions and human IgG1:κ 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 kDa.
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CLINICAL TRIALS

Study Demographics and Trial Design

Rheumatoid Arthritis

The efficacy and safety of HUMIRA[®] (adalimumab) were assessed in five randomized, double-blind studies in patients ≥ 18 years of age with active rheumatoid arthritis diagnosed according to the American College of Rheumatology (ACR) criteria. Patients had at least six swollen and nine tender joints. HUMIRA[®] was administered subcutaneously in combination with methotrexate (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). **Table 8** summarizes the controlled clinical trials that were done in patients with active rheumatoid arthritis.

Table 8. Summary of Controlled Clinical Trials Supporting Safety and Efficacy in Patients with Rheumatoid Arthritis

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Gender (% Female)
RA I	Multicenter, double-blind, randomized, placebo-controlled	HUMIRA [®] 20 mg, 40 mg, or 80 mg; eow	200	54.8 \pm 11.9	75.5
		Placebo Subcutaneous 24 weeks	60	55.2 \pm 10.9	83.3
RA II	Multicenter, double-blind, randomized, placebo-controlled	HUMIRA [®] 20 mg or 40 mg; ew or eow	434	53.0 \pm 12.3	77.4
		Placebo Subcutaneous 26 weeks	110	53.5 \pm 13.2	77.3
RA III	Multicenter, double-blind, randomized, placebo-controlled	HUMIRA [®] 20 mg ew or 40 mg eow	419	56.2 \pm 12.1	75.9
		Placebo Subcutaneous 52 weeks	200	55.6 \pm 12.0	73.0
	Open-label extension	HUMIRA [®] 40 mg eow	553	55.71 \pm 12.02	74.7

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Gender (% Female)
RA IV	Multicenter, double-blind, randomized, placebo-controlled	HUMIRA [®] 40 mg eow	315	55.2 ± 12.7	80.0
		Placebo Subcutaneous 24 weeks	315	55.7 ± 12.4	79.7
RA I to RA IV Combined	Multicenter, double-blind, randomized, placebo-controlled	HUMIRA [®]	1368	54.7 ± 12.3	77.3
		Placebo	685	55.3 ± 12.3	77.7
RA V	Phase 3, multicenter, double-blind, active comparator-controlled, parallel-group	HUMIRA [®] 40 mg eow	274	52.1 ± 13.5	77.4
		HUMIRA [®] 40 mg eow + MTX ew	268	51.9 ± 14.0	72.0
		MTX ew	257	52.0 ± 13.1	73.9
		Subcutaneous and oral 104 weeks			

Definition(s): ew = every week; eow = every other week; MTX = methotrexate

Mean ages across the four studies ranged from 53.0 years (HUMIRA[®] group, Study RA II) to 56.2 years (HUMIRA[®] group, Study RA III). The mean age in Study RA V was 51.9 years (HUMIRA[®] + methotrexate group) to 52.0 years (methotrexate group). Mean weight ranged from 68.5 kg (HUMIRA[®] group, Study RA II) to 80.3 kg (placebo group, Study RA III). The mean weight in Study RA V was 74.4 kg (HUMIRA[®] group) to 76.8 kg (HUMIRA[®] + methotrexate group). As expected, based on the demographics of the disease, patients were predominantly female, with the percentage of female patients ranging from 73.0% (placebo group, Study RA III) to 83.3% (placebo group, Study RA I). Similarly, the percentage of females in Study RA V ranged from 72.0% (HUMIRA[®] + methotrexate group) to 77.4% (HUMIRA[®] group). Patients were predominantly Caucasian, with the percentage of Caucasian patients ranging from 75.0% (placebo group, Study RA I) to 99.1% (placebo group, Study RA II). The percentage of Caucasian patients in Study RA V ranged from 93.3% (HUMIRA[®] + methotrexate group) to 94.2 % (methotrexate group). The high percentage of Caucasian patients in Study RA II was consistent with the populations of the geographic regions in which this study was conducted (i.e., Europe, Canada, and Australia). Overall, the demographic characteristics of the study patients were fairly representative of rheumatoid arthritis in the general population. There were no notable differences between the studies in any of the demographic characteristics analyzed.

Description of Clinical Studies

HUMIRA[®] was evaluated in over 3000 patients in all rheumatoid arthritis clinical trials. Some patients were treated for greater than 60 months duration. The efficacy and safety of HUMIRA[®] were assessed in five randomized, double-blind, well-controlled studies.

Study RA I evaluated 271 patients with moderately to severely active rheumatoid arthritis who had failed therapy with at least one but no more than four DMARDs, and had inadequate response to methotrexate.

Study RA II evaluated 544 patients with moderately to severely active rheumatoid arthritis who had failed therapy with at least one DMARD. Doses of placebo, 20 or 40 mg of HUMIRA[®] were given by subcutaneous injection as monotherapy every other week or weekly for 26 weeks.

Study RA III evaluated 619 patients with moderately to severely active rheumatoid arthritis who had an inadequate response to methotrexate. 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 Week 52. Study RA III had an additional primary endpoint at Week 52 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 five years.

Study RA IV assessed safety in 636 patients with moderately to severely active rheumatoid arthritis 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 moderate to severely active early rheumatoid arthritis (disease duration less than three years) who were ≥ 18 years old and methotrexate naïve. This study compared the efficacy of HUMIRA[®] + methotrexate combination therapy and methotrexate monotherapy in reducing the signs and symptoms and rate of progression of joint damage in rheumatoid arthritis. Patients were randomized to receive HUMIRA[®] 40 mg every other week + methotrexate combination therapy, HUMIRA[®] 40 mg every other week monotherapy, or methotrexate given weekly, for 104 weeks.

Psoriatic Arthritis

The efficacy of HUMIRA[®] was assessed in two randomized, double-blind, placebo-controlled studies in 413 patients. The primary study treated 313 adult patients with moderately to severely active psoriatic arthritis who had an inadequate response to nonsteroidal anti-inflammatory drug (NSAID) therapy. Of the 313 treated in this study, 158 (50.5%) were described as taking methotrexate at the time of randomization. Doses of HUMIRA[®] 40 mg every other week were administered for 24 weeks. **Table 9** summarizes the controlled clinical trials that were done in patients with active psoriatic arthritis.

Table 9. Summary of Controlled Clinical Trials Supporting Safety and Efficacy in Patients with Psoriatic Arthritis

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Gender (% Female)
PsA I	Multicenter, double-blind, randomized, placebo-controlled, stratified by MTX use and extent of psoriasis ($\geq 3\%$ or $< 3\%$ BSA)	HUMIRA [®] 40 mg eow	151	48.6 \pm 12.5	43.7
		Placebo Subcutaneous 24 weeks	162	49.2 \pm 11.1	45.1
PsA II	Multicenter, double-blind, randomized, placebo-controlled, stratified by DMARD use (yes, no)	HUMIRA [®] 40 mg eow	51	50.4 \pm 11.0	43.1
		Placebo Subcutaneous 24 weeks	49	47.7 \pm 11.3	49.0
PsA I and PsA II	Multicenter, double-blind, randomized, placebo-controlled, stratified with MTX (PsA I), and DMARDs (PsA II)	HUMIRA [®] 40 mg eow	202	49.1 \pm 12.2	43.6
		Placebo Subcutaneous 24 weeks	211	48.9 \pm 11.2	46.0

Definition(s): eow = every other week; MTX = methotrexate; BSA = body surface area; DMARDs = disease-modifying anti-rheumatic drugs

Mean ages across the two studies ranged from 47.7 years (placebo group, Study PsA II) to 50.4 years (HUMIRA[®] group, Study PsA II). Mean weight ranged from 85.5 kg (placebo group, Study PsA I) and 91.5 kg (HUMIRA[®] group, Study PsA II). The percentage of females ranged from 43.1 % (HUMIRA[®] group, Study PsA II) and 45.1% (placebo group, Study PsA I). Patients were predominantly Caucasian, with the percentage of Caucasian patients ranging from 93.8% (placebo group, Study PsA I) to 98.0% (HUMIRA[®] group, Study PsA II). There were no notable differences between the studies in any of the demographic characteristics analyzed. Upon completion of both studies, 383 patients enrolled in an open-label extension study (**Table 10**) in which HUMIRA[®] 40 mg is administered every other week.

Table 10. Summary of Open-Label Clinical Trials Evaluating Long-Term Safety and Efficacy in Patients with Psoriatic Arthritis

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range) (Years)	Gender (% Female)
PsA III	Multicenter, open-label, multi-national continuation of studies PsA I and PsA II.	HUMIRA [®] 40 mg eow Subcutaneous 120 weeks or when commercially available, whichever is later	395	49.0 ± 11.7 (20.0 to 88.0)	44.6

Definition(s): eow = every other week

Description of Clinical Studies

Study PsA I evaluated the effectiveness and safety of HUMIRA[®] either alone or in combination with concomitant methotrexate in subjects with moderately to severely active PsA who have had an inadequate response or intolerance to NSAID therapy.

Study PsA II evaluated the effectiveness and safety of HUMIRA[®] either alone or in combination with any concomitant DMARD (except cyclosporine or tacrolimus) in subjects with moderately to severely active psoriatic arthritis who have had an inadequate response to DMARD therapy.

Study PsA III evaluates the long-term safety and efficacy of HUMIRA[®] 40 mg every other week in the treatment of psoriatic arthritis in subjects who completed the controlled Studies PsA I and PsA II.

Ankylosing Spondylitis

The safety and efficacy of HUMIRA[®] 40 mg every other week were assessed in 393 adult patients in two randomized, 24-week double-blind, placebo-controlled studies in patients with active ankylosing spondylitis who have had an inadequate response to or intolerance to one or more NSAIDs, and who may have additionally failed DMARD therapy. The larger study enrolled 315 adult patients with active ankylosing spondylitis [defined as fulfilling at least two of the following three criteria: (1) a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥ 4 cm, (2) a visual analogue score (VAS) for total back pain ≥ 40 mm, and (3) morning stiffness ≥ 1 hour]. The primary efficacy endpoint was percentage of ASAS 20 responders at Week 12 measured by the Assessment in Ankylosing Spondylitis (ASAS) response criteria. Additional pre-determined endpoints included: response as defined by ASAS 5/6 criteria, ASAS 40/50/70 and partial remission, Bath Ankylosing Spondylitis Metrology Index (BASMI), Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). 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 80 weeks.

Crohn's Disease

The safety and efficacy of multiple doses of HUMIRA[®] were assessed in over 1500 patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] \geq 220 and \leq 450) in randomized, double-blind, placebo-controlled studies. Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted and 80% of patients continued to receive at least one of these medications.

Table 11 summarizes the controlled clinical trials and **Table 12** summarizes the open-label clinical trials that were done in patients with moderately to severely active Crohn's disease.

Table 11. Summary of Controlled Clinical Trials Supporting Safety and Efficacy in Patients with Crohn's Disease

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Gender (% Female)
CD I	Randomized, double-blind, placebo-controlled, multicenter, dose ranging study in anti-TNF naïve subjects	HUMIRA [®] 160 mg at Week 0 and 80 mg at Week 2; or HUMIRA [®] 80 mg at Week 0 and 40 mg at Week 2; or HUMIRA [®] 40 mg at Week 0 and 20 mg at Week 2	225	39 ± 12 (18 to 74)	55.6
		Placebo	74	37 ± 13 (19 to 74)	50.0
		Subcutaneous 4 weeks			
CD II	Randomized, double-blind, placebo-controlled, multicenter study in patients who had lost response to or were intolerant to infliximab	HUMIRA [®] 160 mg at Week 0 and 80 mg at Week 2	159	39.4 ± 11.9 (19 to 75)	68.6
		Placebo	166	37.4 ± 11.9 (18 to 75)	60.8
		Subcutaneous 4 weeks			

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Gender (% Female)
CD III	Randomized, double-blind, multicenter, placebo-controlled	<u>Initial Open-Label:</u> HUMIRA [®] 80 mg at Week 0 and 40 mg at Week 2			
		<u>Post-Randomization (Week 4):</u> HUMIRA [®] 40 mg eow	260	36.8 ± 11.5 (17 to 73)	62.7
		HUMIRA [®] 40 mg ew	257	37.8 ± 12.1 (18 to 75)	61.1
		Placebo	261	36.9 ± 11.4 (18 to 75)	62.1
		Not randomized	76	36.1 ± 13.6 (19 to 75)	60.5
		Subcutaneous 56 weeks			
CD VI	Randomized, double-blind, placebo-controlled, multicenter, efficacy and safety study.	Subjects received OL induction therapy of HUMIRA [®] 160/80 mg at weeks 0/2, and were stratified by responder status to HUMIRA [®] 40 mg eow or placebo for up to 52 weeks. At week 52, subjects were switched to OL HUMIRA [®] 40 mg eow for up to an additional 36 weeks.)			
		HUMIRA [®] eow	64	37 (18 to 74)	62.5
		Placebo	65	37 (18 to 67)	63.1

Definition(s): ew = every week; eow = every other week; TNF = tumor necrosis factor; OL =open-label

Table 12. Summary of Open-Label Clinical Trials Supporting Safety and Efficacy in Patients with Crohn's Disease

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Gender (% Female)
CD IV	Open-label extension of placebo-controlled Study CD I	<p>Subjects received OL HUMIRA® 40 mg at baseline (week 0) and week 2. At week 4, patients were assigned to one of three blinded treatment groups (HUMIRA® eow, ew, or placebo) or OL HUMIRA® eow treatment, based on clinical remission status at baseline. After 1 year (week 56), subjects entered long-term extension phase up to more than 5 years (including preceding CD 1 study); those receiving blinded treatment were switched to OL HUMIRA® eow, and those in the OL group continued their OL treatment.</p> <p style="text-align: center;">All</p>	276	39 (18 – 74)	54.7
CD V	Open-label extension of placebo-controlled Studies CD II or CD III	<p>Subjects entering from a blinded cohort were assigned to OL HUMIRA® 40 mg eow; subjects entering the study from an OL cohort continued their previous dosing regimen of eow or ew.</p> <p style="text-align: center;">Study CD III cohort</p> <p style="text-align: center;">Study CD II cohort</p>	467 310	All 38 (17 to 75)	All 62.4

Definition(s): ew = every week; eow = every other week; OL =open-label

Description of Clinical Studies

Induction of clinical remission (defined as CDAI < 150) was evaluated in two studies, Studies CD I and CD II.

In Study CD I, 299 TNF-blocker naïve patients were randomized to one of four treatment groups; the placebo group received placebo at Weeks 0 and 2, the 160/80 group received 160 mg HUMIRA[®] at Week 0 and 80 mg at Week 2, the 80/40 group received 80 mg at Week 0 and 40 mg at Week 2, and the 40/20 group received 40 mg at Week 0 and 20 mg at Week 2.

In Study CD II, 325 patients who had lost response or were intolerant to infliximab were randomized to receive either 160 mg HUMIRA[®] at Week 0 and 80 mg at Week 2 or placebo at Weeks 0 and 2.

Maintenance of clinical remission was evaluated in Study CD III.

In Study CD III, 854 patients received open-label 80 mg HUMIRA[®] at Week 0 and HUMIRA[®] 40 mg at Week 2. At Week 4, subjects were stratified by their responder status and previous anti-tumor necrosis factor (TNF) use (no, yes) and randomized to one of three blinded treatment groups: HUMIRA[®] 40 mg every other week, HUMIRA[®] 40 mg every week or placebo with a total study duration of 56 weeks. Patients in clinical response (decrease in CDAI \geq 70) at Week 4 were stratified and analyzed separately from those not in clinical response at Week 4. Corticosteroid tapering was permitted after Week 8.

Study CD VI assessed mucosal healing in 135 patients; patients received open-label induction therapy of HUMIRA[®] 160/80 mg at weeks 0/2, and were stratified by responder status to HUMIRA[®] 40 mg every other week (eow) or placebo for up to 52 weeks. At Week 52, subjects were switched to open-label HUMIRA[®] 40 mg eow for up to an additional 36 weeks.

Psoriasis

The safety and efficacy of HUMIRA[®] were assessed in over 1600 patients 18 years of age or older with moderate to severe chronic plaque psoriasis who were candidates for systemic therapy or phototherapy in randomized, double-blind, well-controlled studies. **Table 13** summarizes the controlled clinical trials that were done in patients with moderate to severe plaque psoriasis.

Table 13. Summary of Controlled Clinical Trials Supporting Safety and Efficacy in Patients with Psoriasis

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Gender (% Female)
Ps I	<u>Period A</u> : Double-blind, placebo-controlled	<u>Initial Dose</u> HUMIRA [®] 80 mg			

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Gender (% Female)
	<p>treatment period in subjects with moderate to severe chronic plaque psoriasis (PASI \geq 12, BSA \geq 10%); subjects were randomly assigned (2:1) to receive HUMIRA[®] or placebo</p> <p><u>Period B:</u> Open-label treatment period; all subjects who achieved a \geq PASI 75 response at Week 16 received HUMIRA[®]</p> <p><u>Period C:</u> Double-blind, placebo-controlled treatment period; subjects who maintained a \geq PASI 75 response at Week 33 and were originally randomized to active therapy in Period A were rerandomized (1:1) to receive HUMIRA[®] or placebo</p>	<u>Period A - 16 weeks</u>			
		HUMIRA [®] 40 mg eow	814	44.1 \pm 13.2	32.9
		Placebo	398	45.4 \pm 13.4	35.4
		<u>Period B - 17 weeks</u>			
		HUMIRA [®] 40 mg eow	606	43.9 \pm 13.2	30.7
		<u>Period C - 19 weeks</u>			
		HUMIRA [®] 40 mg eow	250	44.3 \pm 13.0	29.6
		Placebo	240	43.4 \pm 13.2	25.4
		Subcutaneous 52 weeks			

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Gender (% Female)
Ps II	Randomized, double-blind, double-dummy, multicenter, placebo- and active-controlled study in subjects with moderate to severe plaque psoriasis (PASI \geq 10, BSA \geq 10%) who were candidates for systemic therapy or phototherapy and had inadequate response to topical therapy	HUMIRA [®] 80 mg followed by 40 mg eow	108	42.9 \pm 12.6	35.2
		Placebo	53	40.7 \pm 11.4	34.0
		MTX capsules (7.5 to 25.0 mg)	110	41.6 \pm 12.0	33.6
		Subcutaneous and oral 16 weeks			
Ps III	Randomized, double-blind, placebo-controlled, multicenter, dose-ranging study in subjects with moderate to severe plaque psoriasis (BSA \geq 5%) and inadequate response to topical therapy	HUMIRA [®] 80 mg followed by 40 mg eow	45	45.8 \pm 11.6	28.9
		HUMIRA [®] 80 mg followed by 40 mg ew	50	43.8 \pm 13.3	34.0
		Placebo	52	43.3 \pm 13.1	34.6
		Subcutaneous 12 weeks			

Definition(s): ew = every week; eow = every other week; MTX = methotrexate; PASI = Psoriasis Area and Severity Index; BSA = body surface area

Across all treatment groups of Study Ps I, the mean baseline Psoriasis Area and Severity Index (PASI) score was 18.9 and the baseline physician's global assessment (PGA) score ranged from "moderate" (52.6%) to "severe" (41.3%) to "very severe" (6.1%).

Across all treatment groups of Study Ps II, the mean baseline PASI score was 19.7 and the baseline PGA score ranged from "mild" (0.4%) to "moderate" (47.8%) to "severe" (45.6%) to "very severe" (6.3%).

Patients participating in all Phase 2 and Phase 3 psoriasis studies were eligible to enrol into an open-label extension trial, where HUMIRA[®] was given for at least an additional 108 weeks. 1468 patients received at least one dose of HUMIRA[®] during the open-label trial. 1018/1468 (69%) patients received adalimumab for a minimum of 108 weeks. Patients from Study Ps I who enrolled into the open-label trial may have received up to 160 weeks of continuous HUMIRA[®] exposure in the first portion of the extension. 183/233 (79%) eligible patients from Study Ps I completed 160 weeks from the first dose of adalimumab in Ps I to the end of the first portion of the extension trial.

Study Results

Rheumatoid Arthritis

Clinical Response

Studies RA I, RA II and RA III

The percent of HUMIRA[®]-treated patients achieving ACR 20/50/70 responses was consistent across all three trials. The results of the three trials are summarized in **Table 14**.

Table 14. ACR Responses in Placebo-Controlled Trials (Percent of Patients)

Response		Study RA I*		Study RA II*			Study RA III*	
		Placebo + MTX N = 60	HUMIRA [®] 40 mg eow + MTX N = 63	Placebo N = 110	HUMIRA [®] 40 mg eow N = 113	HUMIRA [®] 40 mg eow N = 103	Placebo + MTX N = 200	HUMIRA [®] 40 mg eow + MTX N = 207
ACR 20	6 months	13.3%	65.1%**	19.1%	46.0%**	53.4%**	29.5%	63.3%**
	12 months	NA	NA	NA	NA	NA	24.0%	58.9%**
ACR 50	6 months	6.7%	52.4%**	8.2%	22.1%**	35.0%**	9.5%	39.1%**
	12 months	NA	NA	NA	NA	NA	9.5%	41.5%**
ACR 70	6 months	3.3%	23.8%**	1.8%	12.4%**	18.4%**	2.5%	20.8%**
	12 months	NA	NA	NA	NA	NA	4.5%	23.2%**

* Study RA I at Week 24, Study RA II at Week 26, and Study RA III at Weeks 24 and 52

** p < 0.01 for HUMIRA[®] versus placebo

Definition(s): MTX = methotrexate; ACR = American College of Rheumatology

The results of the components of the ACR response criteria for Studies RA II and RA III are shown in **Table 15**. ACR response rates and improvement in all components of ACR response were maintained to Week 104. Over the two years in Study RA III, 24% of HUMIRA[®] patients receiving 40 mg every other week achieved a major clinical response, defined as maintenance of an ACR 70 response over a 6-month period. ACR responses were maintained in similar proportions of patients for up to five years with continuous HUMIRA[®] treatment in the open-label portion of Study RA III.

Table 15. Components of ACR Response in Studies RA II and RA III

Parameter (median)	Study RA II				Study RA III					
	Placebo N = 110		HUMIRA® 40 mg eow N = 103		Placebo + MTX N = 200			HUMIRA® 40 mg eow + MTX N = 207		
	Baseline	Week 26	Baseline	Week 26	Baseline	Week 24	Week 52	Baseline	Week 24	Week 52
Number of tender joints (Scale 0 to 68)	35	26	31	16**	26	15	15	24	8.0*	6.0*
Number of swollen joints (Scale 0 to 66)	19	16	18	10**	17	11	11	18	5.0*	4.0*
Physician global assessment disease activity [†]	7	6.1	6.6	3.7**	6.3	3.5	3.8	6.5	2.0*	1.6*
Patient global assessments disease activity [†]	7.5	6.3	7.5	4.5**	5.4	3.9	4.3	5.2	2.0*	1.8*
Pain [†]	7.3	6.1	7.3	4.1**	6	3.8	4.6	5.8	2.1*	1.9*
Disability index (HAQ) [‡]	2	1.9	1.9	1.5**	1.5	1.25	1.25	1.5	0.75*	0.75*
CRP (mg/dL)	3.9	4.3	4.6	1.8**	1	0.9	0.9	1	0.40*	0.40*

[†] Visual analogue scale; 0 = best; 10 = worst

[‡] Disability index of the Health Assessment Questionnaire (HAQ); 0 = best; 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity

* p < 0.001 for HUMIRA® versus placebo, based on mean change from baseline

Definition(s): MTX = methotrexate; CRP = C-reactive protein

The time course of ACR 20 response for Study RA III is shown in **Figure 2**. In Study RA III, 85% of patients with ACR 20 responses at Week 24 maintained the response at Week 52. The time course of ACR 20 response for Studies RA I and RA II were similar.

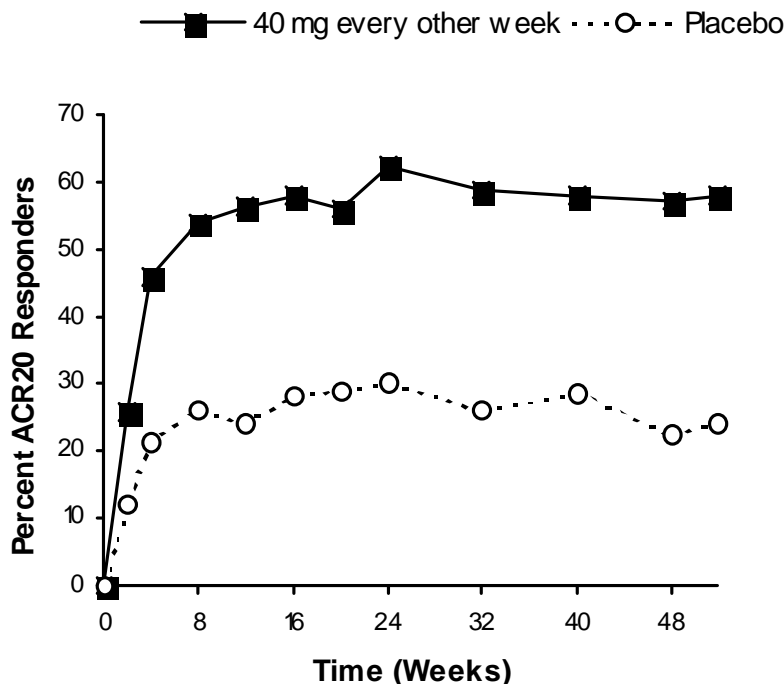


Figure 2. Study RA III ACR 20 Responses Over 52 Weeks

Study RA IV

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[®] and other DMARDs were observed.

In all four studies, HUMIRA[®]-treated patients achieved ACR 20/50/70 responses faster and more often than placebo-treated patients. In Study RA I, there was a statistically significant difference in ACR 20 responses at Week 1 (first study visit) between patients treated with HUMIRA[®] (26.0%) and placebo (5.0%). Statistically significant differences in ACR 20 responses were also seen in Studies RA II, RA III, RA IV at Week 2 (first study visit) between patients treated with HUMIRA[®] (36.4, 29.1 and 33.7%, respectively) and placebo (7.3, 13.0 and 8.6%, respectively). A similar pattern of the time to first ACR 50 and 70 responses was noted in all four studies.

Study RA V

In Study RA V, for early rheumatoid arthritis patients who were methotrexate naïve, the combination therapy with HUMIRA[®] + methotrexate led to faster and significantly greater ACR responses than methotrexate monotherapy at Week 52, and responses were sustained at Week 104. The clinical responses for Study RA V are presented in **Table 16**.

At Week 52, all individual components of the ACR response criteria improved with HUMIRA[®] + methotrexate therapy, and improvements were maintained to Week 104.

Over the two-year study, 48.5% of patients who received HUMIRA[®] + methotrexate combination therapy achieved a major clinical response (ACR 70 for six continuous months) compared to 27.2% of patients who received methotrexate monotherapy ($p < 0.001$).

Table 16. Clinical Responses in Study RA V (All Randomized Subjects)

Response		MTX ^a	HUMIRA ^{®b}	HUMIRA [®] + MTX
		N = 257 (%)	N = 274 (%)	N = 268 (%)
ACR 20	Week 52	62.6	54.4	72.8
	Week 104	56.0	49.3	69.4
ACR 50	Week 52	45.9	41.2	61.6
	Week 104	42.8	36.9	59.0
ACR 70	Week 52	27.2	25.9	45.5
	Week 104	28.4	28.1	46.6
Major Clinical Response ^c		27.2	24.5	48.5

a. $p < 0.05$ for HUMIRA[®] + MTX versus MTX for ACR 20

$p < 0.001$ for HUMIRA[®] + MTX versus MTX for ACR 50 and 70 and Major Clinical Response

b. $p < 0.001$ for HUMIRA[®] + MTX versus HUMIRA[®]

c. Major Clinical Response is achieving ACR 70 response for a continuous six-month period

Definition(s): MTX = methotrexate; ACR = American College of Rheumatology

At Week 52 and Week 104 of treatment in Study RA V, HUMIRA[®] + methotrexate combination therapy was superior to methotrexate monotherapy in achieving a low disease state in patients with recently diagnosed moderate to severe rheumatoid arthritis, as demonstrated by the number of patients who achieved clinical remission [disease activity score (DAS28) < 2.6] at Week 52 and change from baseline in DAS28 at Week 52 and Week 104.

DAS28 responses for Study RA V are presented in **Table 17**.

Table 17. Change in DAS28 from Baseline at Weeks 52 and 104 in Study RA V (All Randomized Subjects)

DAS28		MTX N = 257	HUMIRA [®] N = 274	HUMIRA [®] + MTX N = 268
Week 52	n	184	185	206
	Baseline (mean)	6.3	6.4	6.3
	Change at Week 52 (mean ± SD)	-2.8 ± 1.4 ^a	-2.8 ± 1.5 ^b	-3.6 ± 1.3
	% of subjects in remission (DAS28 < 2.6) at Week 52	20.6% ^a	23.4% ^b	42.9%
Week 104	n	161	158	191
	Baseline (mean)	6.3	6.3	6.3
	Change at Week 104 (mean ± SD)	-3.1 ± 1.4 ^a	-3.2 ± 1.4 ^b	-3.8 ± 1.3
	% of subjects in remission (DAS28 < 2.6) at Week 104	24.9%	25.2%	49.3%

a. p < 0.001 for HUMIRA[®] + MTX versus MTX

b. p < 0.001 for HUMIRA[®] + MTX versus HUMIRA[®]

Definition(s): MTX = methotrexate; DAS = disease activity score; SD = standard deviation

Radiographic Response

In Study RA III, where HUMIRA[®]-treated patients had a mean duration of rheumatoid arthritis of approximately 11 years, 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 12-month results are shown in **Table 18**. HUMIRA[®] + methotrexate-treated patients demonstrated less radiographic progression than patients receiving methotrexate alone at Week 52.

Table 18. Radiographic Mean Changes Over 12 Months in Study RA III with Background Methotrexate

LOCF	Placebo + MTX N = 200	HUMIRA ^{®a} + MTX N = 207	HUMIRA ^{®a} + MTX and Placebo + MTX (95% CI ^{**})	p-value
Change in Modified Total Sharp Score (Mean)	2.7	0.1	-2.6 (1.4, 3.8)	< 0.001*
Change in Erosions (Mean)	1.6	0	-1.6 (0.9, 2.2)	< 0.001
Change in JSN Score (Mean)	1	0.1	-0.9 (0.3, 1.4)	0.002

a. 40 mg administered every other week

* Based on analysis of ranked ANCOVA

** 95% confidence intervals for the differences in change scores between MTX and HUMIRA[®]

Definition(s): MTX = methotrexate; LOCF = last observation carried forward; JSN = joint space narrowing;

CI = confidence interval

In the open-label extension of Study RA III, 77% of the original patients treated with any dose of HUMIRA[®] were evaluated radiographically at two years. Patients maintained inhibition of structural damage, as measured by the TSS; 54% 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 HUMIRA[®] 40 mg every other week have been evaluated radiographically at five years. Patients had continued inhibition of structural damage after three and five years with 65.8 and 58.4% respectively showing no progression of structural damage defined by a change in the TSS ≤ 0.5 .

In Study RA V, HUMIRA[®]-treated patients had a mean duration of rheumatoid arthritis of less than nine months and had not previously received methotrexate. Structural joint damage was assessed radiographically and expressed as change in modified total Sharp score (TSS). The Week 52 results are shown in **Table 19**. A statistically significant difference for change in modified total Sharp score, erosion score and JSN were observed at Week 52 and maintained at Week 104.

Table 19. Radiographic Mean Change (95% Confidence Interval) in Study RA V

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

a. $p < 0.001$ for HUMIRA[®] + MTX versus MTX at Week 52 and Week 104 and for HUMIRA[®] + MTX versus HUMIRA[®] at Week 104

b. $p < 0.01$ for HUMIRA[®] + MTX versus HUMIRA[®] at Week 52

Definition(s): MTX = methotrexate; JSN = joint space narrowing

The percentage of patients without progression (change from baseline in modified total Sharp score ≤ 0.5) was significantly higher with HUMIRA[®] + methotrexate combination therapy compared to methotrexate monotherapy at Week 52 (63.8 and 37.4% respectively, $p < 0.001$) and Week 104 (61.2 and 33.5% respectively, $p < 0.001$).

Quality of Life and Physical Function Response

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

In Study RA III, the mean (CI) improvement in HAQ from baseline at Week 52 was -0.60 (-0.65, -0.55) for the HUMIRA[®] patients and -0.25 (-0.33, -0.17) for placebo + methotrexate ($p < 0.001$) patients. Eighty-two percent (82%) of HUMIRA[®]-treated patients who achieved a 0.5 or greater improvement in HAQ at Week 52 in the double-blind portion of the study maintained that improvement through Week 104 of open-label treatment, and a similar proportion of patients maintained this response through Week 260 (five years). After five years, the proportion of subjects who were HAQ responders at the 0.22, 0.50, 0.75 and 1.0 levels were 76.5, 60.0, 47.5 and 30.8% respectively. Improvement in SF-36 was measured and maintained up to Week 156 (3 years).

In Study RA V, the active comparator-controlled study in early rheumatoid arthritis, the improvement in the HAQ disability index, and the physical component of the SF-36, showed greater improvement ($p < 0.001$) for the HUMIRA[®] + methotrexate combination therapy versus the methotrexate monotherapy at Week 52, which was maintained through Week 104.

At Week 52 and Week 104 of treatment, 69.4% (186/268) and 63.8% (171/268) of subjects, respectively, treated with HUMIRA[®] + methotrexate combination therapy had a decrease

(i.e., improvement) in the disability index of the HAQ of ≥ 0.3 units. In comparison, 61.5% (158/257; $p = 0.562$) and 53.3% (137/257; $p = 0.0146$) of subjects treated with methotrexate monotherapy, and 55.1% (151/274; $p < 0.001$) and 48.2% (132/274; $p < 0.001$) of subjects treated with HUMIRA[®] monotherapy had a decrease in the disability index of the HAQ of ≥ 0.3 units at Weeks 52 and 104, respectively.

Psoriatic Arthritis

Clinical Response

Studies PsA I, PsA II and PsA III

HUMIRA[®] was superior to placebo in all measures of disease activity ($p < 0.001$) as shown in **Table 20** and **Table 21**. Among patients with psoriatic arthritis who received HUMIRA[®], the clinical responses were apparent at the time of the first visit (Week 2), significant at Week 12, and maintained at Week 24 in the double-blind period of the study. **Table 23** presents data from the ongoing open-label study regarding improvement in arthritic manifestations of psoriatic arthritis.

Patients with a psoriasis involvement of at least three percent body surface area (BSA) were evaluated for Psoriatic Area and Severity Index (PASI) responses. In these patients, the skin lesions of psoriasis were improved with HUMIRA[®], relative to placebo, as measured by the PASI. Results were similar with and without concomitant methotrexate therapy. The small number of patients with moderate to severe psoriasis requires additional data to adequately assess the PASI response.

Table 20. ACR and PASI Response in Placebo-Controlled Psoriatic Arthritis Study (Study PsA I) (Percent of Patients)

Response		Placebo N = 162	HUMIRA ^{®†} N = 151
ACR 20	Week 12	14%	58%
	Week 24	15%	57%
ACR 50	Week 12	4%	36%
	Week 24	6%	39%
ACR 70	Week 12	1%	20%
	Week 24	1%	23%
Response		Placebo N = 69	HUMIRA ^{®†} N = 69
PASI 50	Week 12	15%	72%
	Week 24	12%	75%
PASI 75	Week 12	4%	49%
	Week 24	1%	59%

† p < 0.001 for all comparisons between HUMIRA[®] and placebo

Definition(s): ACR = American College of Rheumatology; PASI = Psoriasis Area and Severity Index

Table 21. Components of Disease Activity in Psoriatic Arthritis (Study PsA I)

Parameter mean (median)	Placebo [†] N = 162		HUMIRA ^{®†‡} N = 151	
	Baseline	Week 24	Baseline	Week 24
Number of tender joints (Scale 0 to 78)	25.8 (23.0)	22.3 (17.0)	23.3 (19.0)	11.8 (5.0)
Number of swollen joints (Scale 0 to 76)	14.6 (11.0)	12.1 (8.0)	13.4 (10.0)	7.6 (3.0)
Physician global assessment ^a	53.2 (53.0)	46.0 (48.0)	53.5 (54.0)	21.4 (16.0)
Patient global assessment ^a	47.2 (49.0)	47.6 (49.0)	47.5 (48.0)	24.2 (18.5)
Pain ^a	47.6 (47.5)	47.9 (49.0)	50.6 (53.0)	25.4 (19.0)
Disability index (HAQ) ^b	1.0 (1.0)	0.9 (0.8)	1.0 (0.9)	0.6 (0.4)
CRP (mg/dL) ^c	1.4 (0.8)	1.4 (0.7)	1.4 (0.8)	0.5 (0.2)

† As observed analysis presented, N at Week 24 may be less than 162 for placebo or 151 for HUMIRA[®]

‡ p < 0.001 for HUMIRA[®] versus placebo comparisons based on mean change from baseline

a. Visual analogue scale; 0 = best, 100 = worst

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

c. C-reactive protein (CRP) normal range: 0 to 0.287 mg/dL

Radiographic Response

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

Week 24

The mean change in modified total Sharp score was evaluated and demonstrated that HUMIRA[®]-treated patients had significantly less progression in their X-rays, compared to placebo-treated patients. As shown in **Table 22**, the mean change from baseline in both the erosion and the joint space narrowing scores in the HUMIRA[®] treatment group was significantly superior to placebo. As with other TNF agents, the median change in Sharp scores for both patient groups were zero.

Table 22. Radiographic Mean Changes at Week 24 in Placebo-Controlled Psoriatic Arthritis Study (Study PsA I)[†]

Response	Placebo N = 152	HUMIRA [®] N = 144	p-value
Total Sharp score	1	-0.2	< 0.001
Erosion score	0.6	0	< 0.001
JSN score	0.4	-0.2	< 0.001

[†] Analysis of patients with X-ray films at both baseline and Week 24
Definition(s): JSN = joint space narrowing

Week 48

HUMIRA[®]-treated patients demonstrated greater inhibition of radiographic progression at Week 48 compared to placebo-treated patients at Week 24 (see **Table 23**).

Table 23. Change in Modified Total Sharp Score[‡] in Psoriatic Arthritis (Study PsA III)

Response		Placebo	HUMIRA [®]	
		N = 141	N = 133	
		Week 24	Week 24	Week 48
Modified Total Sharp Score	Baseline mean	22.1	23.4	23.4
	Mean change ± SD	0.9 ± 3.06	-0.1 ± 1.69**	0.1 ± 2.74**
	Change (range)	-3.5 to 22.0	-6.8 to 12.5	-5.9 to 24.2
Erosion Score	Baseline mean	11.8	12.4	12.4
	Mean change ± SD	0.5 ± 1.91	0.0 ± 0.91**	0.1 ± 1.79*
	Change (range)	-2.2 to 14.5	-2.2 to 7.5	-4.4 to 16.5
JSN score	Baseline mean	10.4	11.0	11.0
	Mean change ± SD	0.4 ± 1.60	-0.1 ± 1.06**	0.0 ± 1.33**
	Change (range)	-3.5 to 10.2	-5.7 to 5.0	-4.0 to 7.7

* p < 0.05 for the difference between HUMIRA[®], Week 48 and placebo, Week 24 (primary analysis)
** p < 0.001 for the difference between HUMIRA[®], Week 48 and placebo, Week 24 (primary analysis)
‡ X-rays with less than 50% assessments were imputed
Definition(s): JSN = joint space narrowing; SD = standard deviation

Physical Function Response

Disability and physical function were assessed in psoriatic arthritis study using Health Assessment Questionnaire Disability Index (HAQ-DI). The HUMIRA[®]-treated patients had significantly greater improvement in the disability index of the HAQ from baseline to Week 24, compared to placebo and were maintained up to Week 84 (see **Table 24** and **Table 25**).

Table 24. Disability Index of the HAQ (Full Analysis Set) (Study PsA I)

Disability Index of the HAQ		Placebo		HUMIRA [®] 40 mg eow		p-value ^a
		N = 162		N = 151		
		N	Mean ± SD	N	Mean ± SD	
Week 12	Baseline	154	1.0	142	1.0	< 0.001*
	Change Observed	154	-0.1 ± 0.45	142	-0.4 ± 0.45	
Week 24	Baseline	145	1.0	141	1.0	< 0.001*
	Change Observed	145	-0.1 ± 0.42	141	-0.4 ± 0.49	

* Statistically significant at the p = 0.001 level

a. p-value for differences between treatment groups from an ANOVA model with treatment group and baseline methotrexate use/extent of psoriasis (≥ 3% BSA, < 3% BSA) as factors

Definition(s): HAQ = Health Assessment Questionnaire; BSA = body surface area; eow = every other week; SD = standard deviation

Table 25. Mean Change From Baseline in Disability Index of HAQ by Visit (Observed) (Study PsA I Subjects Randomized to HUMIRA®)

Visit	N	Baseline ^a Mean	Visit Mean	Change from Baseline		
				Mean	Standard Deviation	Range (Min to Max)
Week 24	137	1.0	0.6	-0.4	0.48	-1.8 to 1.1
Week 26	137	1.0	0.5	-0.4	0.50	-2.1 to 0.9
Week 30	137	1.0	0.6	-0.4	0.49	-1.9 to 1.0
Week 36	137	1.0	0.6	-0.4	0.50	-1.9 to 1.1
Week 42	135	1.0	0.6	-0.4	0.50	-1.9 to 1.0
Week 48	134	1.0	0.6	-0.4	0.54	-2.3 to 0.9
Week 60	132	1.0	0.5	-0.4	0.49	-1.9 to 0.6
Week 72	129	1.0	0.6	-0.4	0.49	-1.9 to 0.6
Week 84	79	0.9	0.5	-0.4	0.49	-1.9 to 0.8

Note: The disability index of the Health Assessment Questionnaire (HAQ) has a range from 0 to 3 with a higher score indicating a greater extent of functional limitations

a. Last assessment prior to the first HUMIRA® injection

A subset of the subjects is still being followed in the ongoing study.

Results from the Short Form Health Survey (SF-36) support these findings, with statistically significant Physical Component Summary (PCS) scores, as well as statistically significant pain and vitality domain scores at Week 24, which were maintained to Week 72.

Ankylosing Spondylitis

Clinical Response

Results showed statistically significant reduction in signs and symptoms of ankylosing spondylitis in patients treated with HUMIRA® compared to placebo in Study AS I. Significant improvement in measures of disease activity was first observed at Week 2 and maintained through Week 24 as shown in **Figure 3** and **Table 26**.

Patients with total spinal ankylosis were included in the larger study (n = 11). Responses of these patients were similar to those without total ankylosis.

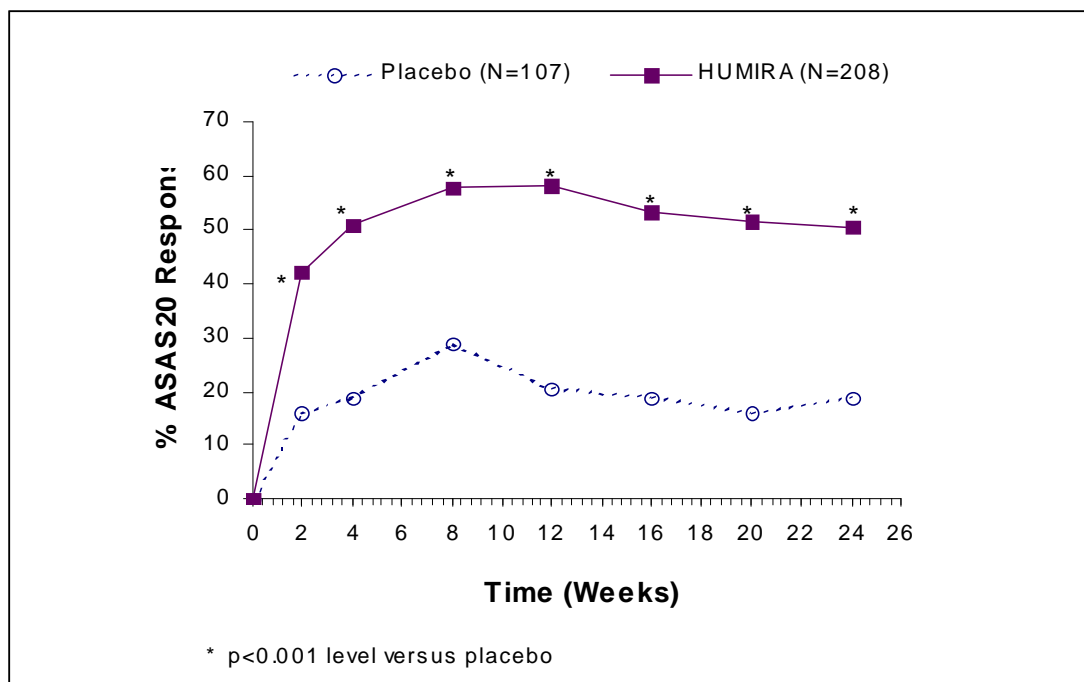


Figure 3. ASAS 20 Response by Visit, Study AS I

At Week 12, 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 ($p < 0.001$). At Week 24, the ASAS 20/50/70 responses were achieved by 51, 35 and 24%, respectively, of patients receiving HUMIRA[®], compared to 19, 11, and 8%, respectively, of patients receiving placebo ($p < 0.001$). These results were sustained in patients receiving open-label HUMIRA[®] through Week 52.

In a sub-group analysis by region an HUMIRA[®] versus placebo treatment group difference was observed between the United States (US) and European (EU) subjects (21.7 and 50.9% respectively). This difference in the treatment effect is driven by the different placebo ASAS 20 response rates (33.3% for US versus 10.2% for EU). However, the HUMIRA[®] ASAS 20 response rates were 55 and 61.1% in the US and EU respectively.

A low level of disease activity [defined as a value < 20 (on a scale of 0 to 100 mm) in each of the four ASAS response parameters] was achieved at Week 24 in 22% of HUMIRA[®]-treated patients versus 6% in placebo-treated patients ($p < 0.001$).

Other secondary and additional measures of efficacy such as response as defined by ASAS 5/6 criteria, ASAS 40, metrology (BASMI), enthesitis (MASES), and disease activity (BASDAI) were statistically significant at Weeks 12 and 24.

Table 26. Components of Ankylosing Spondylitis Disease Activity in Study AS I

Parameters	Placebo N = 107		HUMIRA® N = 208	
	Baseline Mean	Week 24 Mean	Baseline Mean	Week 24 Mean
ASAS 20 Response Criteria*				
Patient's Global Assessment of Disease Activity ^a	65	60	63	38
Total Back Pain	67	58	65	37
Inflammation ^b	6.7	5.6	6.7	3.6
BASFI	56	51	52	34
BASDAI* Score	6.3	5.5	6.3	3.7
CRP*	2.2	2	1.8	0.6

a. Percent of subjects with at least a 20% and 10-unit improvement measured on a visual analogue scale (VAS) with 0 = "none" and 100 = "severe"

b. Mean of questions 5 and 6 of BASDAI

* Statistically significant as $p < 0.001$ for all comparisons between HUMIRA® and placebo at Week 24

Definition(s): BASFI = Bath Ankylosing Spondylitis Functional Index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CRP = C-reactive protein (mg/dL)

Similar results (not all statistically significant) were seen in the second randomized trial, a multicenter, double-blind, placebo-controlled study of 82 patients with ankylosing spondylitis (Study AS II).

Patients treated with HUMIRA® achieved statistically significant greater improvement from baseline in the Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL) score (-3.15 versus -0.95, $p < 0.001$) and in the Short Form Health Survey (SF-36) Physical Component Summary (PCS) score (6.93 versus 1.55, $p < 0.001$) compared to placebo-treated patients at Week 12, which were maintained through Week 24.

Crohn's Disease

Clinical Responses

Studies CD I and CD II

A statistically significantly greater percentage of the patients treated with HUMIRA® 160/80 mg achieved induction of clinical remission versus placebo at Week 4 regardless of whether the patients were TNF-blocker naïve (Study CD I) or had lost response or are intolerant to infliximab (Study CD II) (**Table 27** and **Table 28**, respectively).

The percentage of subjects who achieved clinical remission with HUMIRA® 160/80 mg induction therapy was greater for those receiving corticosteroids versus those who did not.

Table 27. Induction of Clinical Remission and Response in Infliximab Naïve Patients (Study CD I) (Percent of Patients)

Response		Placebo N = 74	HUMIRA® 160/80 mg N = 76
Week 4	Clinical remission	12%	36%*
	Difference ^a (95% CI)		23.4 (10.3, 36.4)
	Clinical response (CR-100)	24%	49%**
	Difference ^a (95% CI)		24.4 (9.5, 39.3)
Week 4	Clinical response (CR-70)	34%	58%**
	Difference ^a (95% CI)		24.1 (8.6, 39.6)

All p-values are pairwise comparisons of proportions for HUMIRA® versus placebo

* p < 0.001

** p < 0.01

a. Difference refers to the difference between the proportion (%) of HUMIRA®-treated subjects achieving clinical remission and clinical response compared with the placebo-treated subjects; 95% CI based on normal approximation of the binomial

Definition(s): CI = confidence interval; Clinical remission = Crohn's Disease Activity Index (CDAI) score < 150; Clinical response 100 (CR-100) and a clinical response 70 (CR-70) = decreases from baseline in CDAI scores of at least 100 points and at least 70 points, respectively

Table 28. Induction of Clinical Remission and Response in Infliximab Experienced Patients (Study CD II) (Percent of Patients)

Response		Placebo N = 166	HUMIRA® 160/80 mg N = 159
Week 4	Clinical remission	7%	21%*
	Difference ^a (95% CI)		14.2 (6.7, 21.6)
Week 4	Clinical response (CR-100)	25%	38%**
	Difference ^a (95% CI)		13.7 (3.7, 23.7)
Week 4	Clinical response (CR-70)	34%	52%**
	Difference ^a (95% CI)		17.8 (7.3, 28.4)

p-values are pairwise comparisons of proportions for HUMIRA® versus placebo

* p < 0.001

** p < 0.01

a. Difference refers to the difference between the proportion (%) of HUMIRA®-treated subjects achieving clinical remission and clinical response compared with the placebo-treated subjects; 95% CI based on normal approximation of the binomial

Definition(s): CI = confidence interval; Clinical remission = Crohn's Disease Activity Index (CDAI) score < 150; Clinical response 100 (CR-100) and a clinical response 70 (CR-70) = decreases from baseline in CDAI scores of at least 100 points and at least 70 points, respectively

Clinical Remission at Week 4 by baseline predictors in infliximab experienced patients is presented in **Table 29**.

Table 29. Clinical Remission at Week 4 by Baseline Predictors in Infliximab Experienced Patients (Study CD II)

Baseline Predictors		Placebo N = 166	HUMIRA® 160/80 mg N = 159
Corticosteroid User		3/73 (4.1)	18/55 (32.7)
Corticosteroid Nonuser		9/93 (9.7)	16/104 (15.4)
Aminosalicylate User		6/60 (10.0)	6/45 (13.3)
Aminosalicylate Nonuser		6/106 (5.7)	28/114 (24.6)
CDAI Score	≤ 300	8/81 (9.9)	24/75 (32.0)
	> 300	4/85 (4.7)	10/84 (11.9)

Definition(s): CDAI = Crohn's disease activity index

Study CD III

At Week 4, 58% (499/854) of patients were in clinical response and were assessed in the primary analysis. Of those in clinical response at Week 4, 48% had been previously exposed to other anti-TNF therapy. At Weeks 26 and 56, statistically significantly greater proportions of patients who were in clinical response at Week 4 achieved clinical remission in the HUMIRA® maintenance groups compared to patients in the placebo maintenance group (**Table 30**).

Table 30. Maintenance of Clinical Remission and Response (Percent of Patients) (Study CD III)

Response		Placebo N = 170	HUMIRA® 40 mg eow N = 172	HUMIRA® 40 mg ew N = 157
Week 26	Clinical remission	17%	40%*	47%*
	Difference ^a (95% CI)		22.5 (13.2, 31.7)	29.4 (19.8, 39.1)
	Clinical response (CR-100)	27%	52%*	52%*
Week 56	Clinical response (CR-100)	27%	52%*	52%*
	Difference ^a (95% CI)		25.3 (15.3, 35.3)	25.8 (15.5, 36.0)
	Clinical response (CR-70)	28%	54%*	56%*
Week 56	Clinical response (CR-70)	28%	54%*	56%*
	Difference ^a (95% CI)		25.8 (15.8, 35.9)	27.8 (17.5, 38.1)
	Clinical remission	12%	36%*	41%*
Week 56	Clinical remission	12%	36%*	41%*
	Difference ^a (95% CI)		24.3 (15.6, 32.9)	29.6 (20.5, 38.7)
	Clinical response (CR-100)	17%	41%*	48%*
Week 56	Clinical response (CR-100)	17%	41%*	48%*
	Difference ^a (95% CI)		24.8 (15.6, 34.0)	31.3 (21.7, 40.9)
	Clinical response (CR-70)	18%	43%*	49%*
Week 56	Clinical response (CR-70)	18%	43%*	49%*
	Difference ^a (95% CI)		25.4 (16.9, 34.7)	31.4 (21.7, 41.1)

Response	Placebo N = 170	HUMIRA [®] 40 mg eow N = 172	HUMIRA [®] 40 mg ew N = 157
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* p < 0.001 for HUMIRA[®] versus placebo pairwise comparisons of proportions

a. Difference refers to the difference between the proportion (%) of HUMIRA[®]-treated subjects achieving clinical remission and clinical response compared with the placebo-treated subjects; 95% CI based on normal approximation of the binomial

Definition(s): eow = every other week; ew = every week; CI = confidence interval; Clinical remission = Crohn's Disease Activity Index (CDAI) score < 150; Clinical response 100 (CR-100) and clinical response 70 (CR-70) = decreases from baseline in CDAI scores of at least 100 points and at least 70 points, respectively

More patients receiving HUMIRA[®] maintenance therapy were able to achieve remission and discontinue corticosteroids for at least 90 days than those receiving placebo at Week 26 (19% HUMIRA[®] every other week and 15% HUMIRA[®] every week versus 3% placebo, p < 0.02) and at Week 56 (29% HUMIRA[®] every other week and 20% HUMIRA[®] every week versus 5% placebo, p < 0.01).

In Study CD III, 117 patients had at least one draining fistula at Baseline and Screening. Of those, 23 out of 70 in the HUMIRA[®] group (both regimens) and 6 out of 47 in the placebo group had no draining fistula at the last two evaluations.

Of those in response at Week 4 who attained remission during the study, patients in the HUMIRA[®] maintenance groups maintained remission for a significantly longer time than patients in the placebo maintenance group (**Figure 4**).

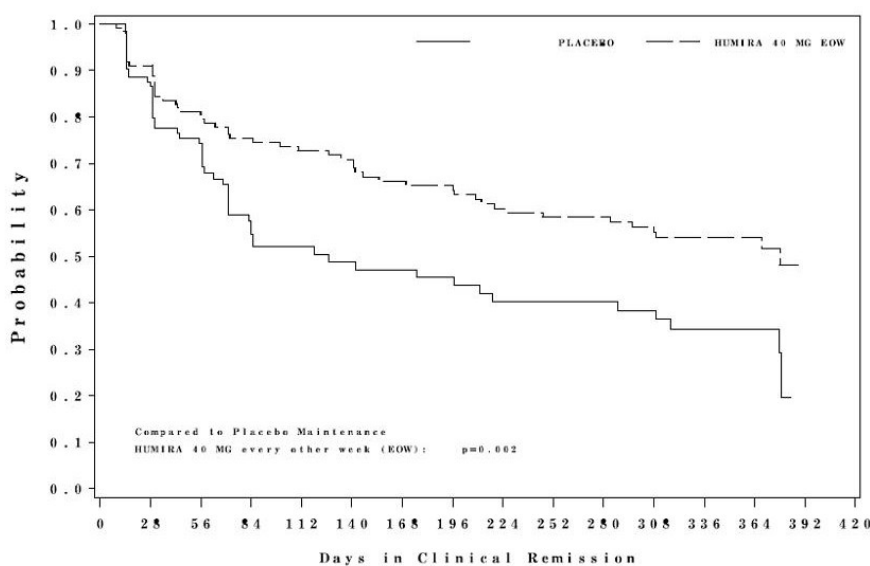


Figure 4. Days in Clinical Remission for Patients Who Had Achieved Clinical Remission (Induction Period) by Week 4 in Study CD III

Some patients who experience decrease in their response may benefit from an increase in dose to HUMIRA[®] 40 mg every week. Supportive evidence for a restoration of clinical response as a result of dose escalation was derived from the modified-intent-to treat (mITT) Analysis Set of Study CD III in subjects who initially responded but lost response to HUMIRA[®] 40 mg every other week dosing. In those subjects who responded at Week 4, were in remission at Week 12 but lost remission after Week 12, and were dose escalated to HUMIRA[®] 40 mg every week (n = 14), clinical remission was restored in 71% (10/14) of these subjects, with median time to restored clinical remission of 9 weeks.

Some patients who have not responded by Week 4 (induction period) may benefit from continued maintenance therapy through Week 12. Available data suggest that the clinical response is usually achieved at Week 4 of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

Symptoms, overall well-being and functioning were assessed using the Inflammatory Bowel Disease Questionnaire (IBDQ). Treatment with HUMIRA[®] resulted in statistically significant improvements in IBDQ total score which measures bowel symptoms, systemic symptoms, emotional well-being and social functioning, compared with placebo (p < 0.001) at Week 4 in Studies CD I and CD II and Weeks 26 and 56 in Study CD III.

Study CD VI

An endoscopy study (n=135) assessed rates of mucosal healing in patients with moderate to severe Crohn's Disease given either HUMIRA[®] or placebo. After 8 weeks of randomised treatment (Week 12 of study), although the results were not statistically significant (p = 0.056), there was a trend towards higher levels of mucosal healing in subjects given HUMIRA[®] compared with subjects given placebo (mucosal healing in 27.4% (17/62) HUMIRA[®] vs 13.1% (8/61) given placebo. In this study, the placebo group received open-label HUMIRA[®] induction therapy.

Psoriasis

Clinical Response

In Studies Ps I, Ps II and Ps III, the primary endpoint was the proportion of patients who achieved a reduction in PASI score of at least 75% (PASI 75) from baseline at Week 16 for Studies Ps I and Ps II and Week 12 for Study Ps III. Other evaluated outcomes in Studies Ps I, Ps II, and Ps III included the PGA and other PASI measures.

Study Ps I had an additional primary endpoint of loss of adequate response after Week 33 and on or before Week 52. Loss of adequate response is defined as a PASI score after Week 33 and on or before Week 52 that resulted in a < PASI 50 response relative to baseline with a minimum of a 6-point increase in PASI score relative to Week 33.

In Study Ps I, response to HUMIRA[®] was rapid, with significantly greater improvements compared to placebo in mean percentage PASI, PASI 75/90 response rates, and PGA clear or minimal scores by Week 4, the first study visit (all p <0.001 vs. placebo).

In Studies Ps I and Ps II, more patients randomized to HUMIRA[®] than to placebo achieved at least a 75% reduction from baseline of PASI score at Week 16 (see **Table 31** and **Table 32**). Other relevant clinical parameters, including PASI 90, PASI 100 (corresponding to a complete clearance of psoriasis skin signs) and PGA of “clear or minimal,” were also improved over placebo.

In Study Ps II, superior results were achieved for PASI 75, PASI 90, PASI 100 and PGA of “clear or minimal” in patients randomized to the HUMIRA[®] treatment group versus those randomized to receive methotrexate.

Table 31. Psoriasis Study Ps I Efficacy Results at Week 16 (Percent of Patients)

Response	Placebo N = 398	HUMIRA [®] 40 mg eow N = 814
≥ PASI 75	6.5%	70.9% ^a
≥ PASI 90	1.8%	45.0% ^a
PASI 100	0.8%	20.0% ^a
PGA: Clear/minimal	4.3%	62.2% ^a

a. p < 0.001 for HUMIRA[®] versus placebo

Definition(s): eow = every other week; PASI = Psoriasis Area Severity index; PGA = physician’s global assessment

Table 32. Psoriasis Study Ps II Efficacy Results at Week 16 (Percent of Patients)

Response	Placebo N = 53	MTX N = 110	HUMIRA [®] 40 mg eow N = 108
≥ PASI 75	18.9%	35.5%	79.6% ^{a,b}
≥ PASI 90	11.3%	13.6%	51.9% ^{a,b}
PASI 100	1.9%	7.3%	16.7% ^{a,b}
PGA: Clear/minimal	11.3%	30.0%	73.1% ^{a,b}

a. p < 0.001 for HUMIRA[®] versus placebo

b. p < 0.001 for HUMIRA[®] versus methotrexate

Definition(s): MTX = methotrexate; eow = every other week; PASI = Psoriasis Area Severity index; PGA = physician’s global assessment

PASI 75, PASI 90 and PASI 100 Responses from Week 0 to Week 24 for Study Ps I are presented in **Figure 5**.

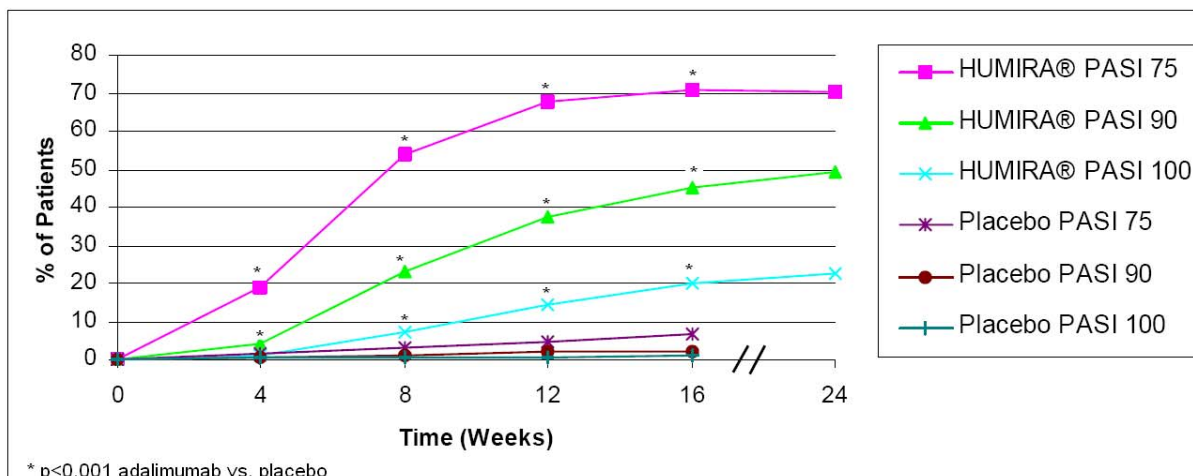


Figure 5. Psoriasis Study Ps I Response Rate from Week 0 to Week 24

Results from Study Ps III supported the efficacy demonstrated in Studies Ps I and Ps II.

In Study Ps I, patients who were PASI 75 responders and were re-randomized to continue HUMIRA® therapy at Week 33 were less likely to experience a loss of adequate response on or before Week 52 than the PASI 75 responders who were re-randomized to placebo at Week 33 (4.9% versus 28.4%, $p < 0.001$).

A total of 233 PASI 75 responders at Week 16 and Week 33 received continuous HUMIRA® therapy for 52 weeks in Psoriasis Study I, and continued HUMIRA® in the open-label extension trial. The proportion of patients with full skin clearance (PASI 100) was generally maintained through Week 108 [31.8% at OLE entry ($n=74/233$); 30.1% at Week 108 ($n=69/229$ (total of 160 weeks))].

A total of 94 patients were randomized to HUMIRA® therapy in Psoriasis Study II, and continued HUMIRA® in the open label extension trial. The proportion of patients with PASI 75 after an additional 108 weeks of open-label therapy was 58.1% ($n=54/93$) (total of 124 weeks).

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 [95% C.I. (127, 146 days)]. None of these patients experienced rebound during the withdrawal period. A total of 76.5% (218/285) of patients who entered the retreatment period had a response of PGA “clear” or “minimal” after 16 weeks of retreatment, 69.1% (123/178) for patients who relapsed and 88.8% (95/107) for patients who did not relapse during the withdrawal period.

In the open-label extension study, 349/1256 (27.8%) patients dose escalated from 40 mg every other week to 40 mg weekly due to a PASI response below 50% and were evaluated 12 weeks after dose escalation, and 93/349 (26.6%) patients achieved PASI 75 response.

There were no clinical trials conducted to evaluate the efficacy and safety of HUMIRA® in psoriatic arthritis subjects with both active arthritis and moderate to severe psoriasis.

Quality of Life

Patient Reported Outcomes (PRO) were evaluated by several measures. Quality of Life was assessed using the disease-specific Dermatology Life Quality Index (DLQI) in Study Ps I and Study Ps II

In Study Ps I, patients receiving HUMIRA® demonstrated clinically meaningful improvement in the DLQI total score, disease severity, pain, and pruritus compared to the placebo group at both Weeks 4 and 16. The DLQI result was maintained at Week 52.

In Study Ps II, patients receiving HUMIRA® demonstrated clinically meaningful improvement in the DLQI total score, disease severity, and pruritus compared to the placebo and methotrexate groups at Week 16, and clinically meaningful improvement in pain compared to the placebo group at Week 16.

The Short Form Health Survey (SF-36) was used to assess general health-related quality of life in Study Ps I. The HUMIRA®-treated patients had significantly greater improvement in the SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores.

Comparative Bioavailability Studies

A Phase 1, single-dose, open-label, randomized study conducted to evaluate the bioavailability, safety and tolerability of a single-dose subcutaneous administration of HUMIRA® in the abdomen and thigh via an autoinjector compared to that of administration from a prefilled syringe, demonstrated comparable bioavailability of the autoinjector and the prefilled syringe (**Table 33**).

Table 33. Comparative Bioavailability of HUMIRA® After a Single Subcutaneous Dose Administered via an Autoinjector Versus Administration via a Prefilled Syringe

From Measured Data Uncorrected for Potency				
Geometric Mean ^{&}				
Arithmetic Mean (CV %)				
Parameter	Test* (Regimen A)	Reference [†] (Regimen B)	Point Estimate	90% Confidence Interval
AUC ₀₋₃₆₀ (mcg•h/mL)	1186 1260 (28)	1225 1276 (29)	0.968	0.904 – 1.036
AUC ₀₋₁₃₄₄ (mcg•h/mL)	2249 2454 (33)	2390 2544 (37)	0.941	0.865 – 1.025
C _{max} (mcg/mL)	4.52 4.815 (32)	4.63 4.815 (30)	0.978	0.915 – 1.044
T _{max} [§] (h)	-- 142.3 (54)	-- 151.4 (58)		

* Regimen A: HUMIRA® 40 mg administered subcutaneously via an autoinjector
† Regimen B: HUMIRA® 40 mg administered subcutaneously via a prefilled syringe
§ Expressed as the arithmetic mean (CV%) only
& Antilogarithm of the least squares means for logarithm from analysis of covariance

DETAILED PHARMACOLOGY

General

HUMIRA® (adalimumab) was evaluated in a series of safety pharmacology studies conducted in standard animal models. Adalimumab was shown to have no biologically relevant activity on behavioral / central nervous system, cardiovascular / respiratory, gastrointestinal, genitourinary, hemolytic / coagulation or local anesthetic parameters. A slight prolongation of hexobarbital-induced sleep time noted at high doses in male mice is thought to be of no toxicological relevance.

Pharmacodynamics

By use of multiple in vivo and in vitro preclinical systems, the preclinical pharmacology program demonstrated that adalimumab has a high and specific affinity to human TNF, demonstrates potency for TNF neutralization, and is highly effective in preventing polyarthritis in a transgenic human-TNF mouse model.

In a series of in vitro studies employing sensitive BIAcore technology and competitive receptor binding experiments, the affinity of adalimumab for human TNF was demonstrated to be high. Adalimumab was also shown to bind to pro-TNF. Further, adalimumab neutralized the biological

effects of TNF in cell cytotoxicity and cell activation assays. Adalimumab has specific affinity to human TNF, but does not bind to other tested TNF family members or cytokines.

Adalimumab drug substance batch AFP810 is a typical batch produced by an extended-batch cell culture process (C2-extended, also referred to as CHO-2b in some reports). Previous adalimumab was derived from an early D8E clone and was produced by a repeated-batch fermentation process (C1-repeated, also referred to as CHO-1 in some reports). AFP704 is a typical batch from this earlier manufacturing process. A study was conducted to compare drug substance batch AFP704 and drug substance batch AFP810 in in vitro and in vivo assays. The sensorgrams for the two batches of adalimumab are presented in **Figure 6**.

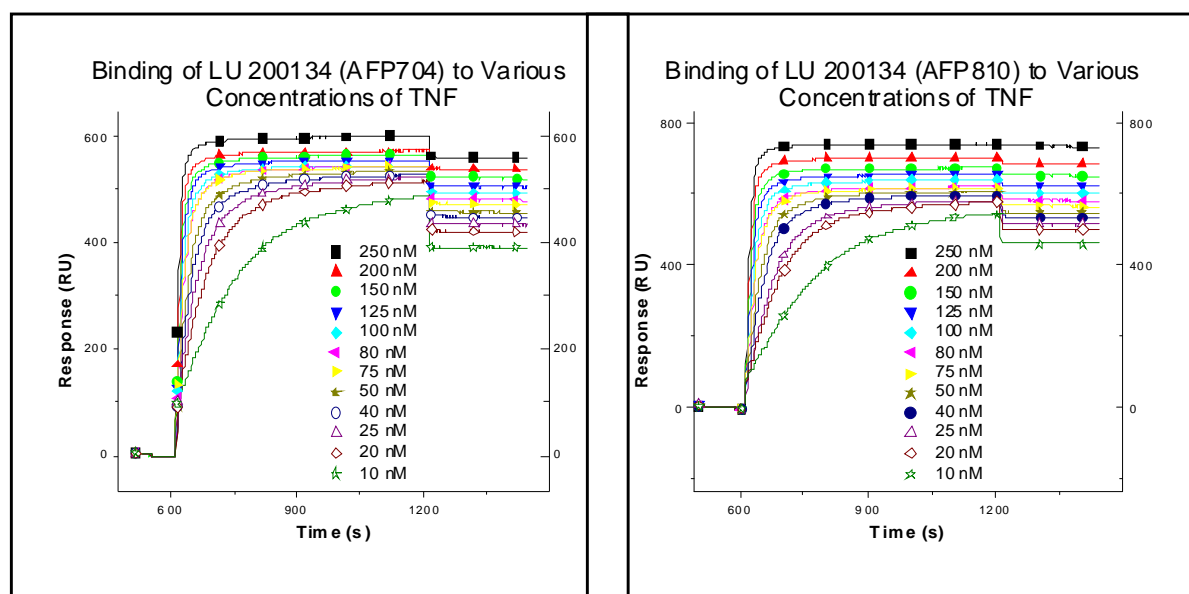


Figure 6. Binding Sensorgrams of Adalimumab Batches AFP704 and AFP810

Parameters of apparent kinetic rate constants of binding between adalimumab and TNF are listed in **Table 34**.

Table 34. Apparent Kinetic Rate Constants for Binding of TNF to Adalimumab Batches

	AFP704 (C1-repeated)	AFP810 (C2-extended)	Average*
k_d , off-rate	$3.31 \times 10^{-5} \text{ s}^{-1}$	$4.58 \times 10^{-5} \text{ s}^{-1}$	$3.95 \times 10^{-5} \text{ s}^{-1}$
k_a , on-rate	$5.82 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$	$5.37 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$	$5.60 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$
K_d	--	--	$7.05 \times 10^{-11} \text{ M}$

* K_d was determined based on the average off and on-rate constant values

Both the apparent kinetic rate constants and the derived dissociation constants (K_d) of the two batches of adalimumab were very similar. An average dissociation constant of 7.05×10^{-11} M indicates that adalimumab has a high affinity for TNF. Furthermore, the average dissociation rate constant (K_d) of $3.95 \times 10^{-5} \text{ s}^{-1}$ corresponds to approximately five hours of adalimumab:TNF complex half-life, which may be beneficial for safe removal of the TNF:adalimumab complex from circulation.

The specificity of adalimumab for TNF from different species was investigated in an L929 bioassay. The order of magnitude of adalimumab neutralization potency for human, chimpanzee, rhesus, *cynomolgus*, marmoset, baboon, and canine TNF was similar (see **Table 35**).

Table 35. TNF Species Specificity of Adalimumab

TNF	Source	Adalimumab IC ₅₀ M
Murine	Recombinant	$> 2.0 \times 10^{-7}$
Rat	Recombinant	$\gg 1.0 \times 10^{-6}$
Rabbit	LPS-stimulated PBMC	1.5×10^{-6}
Porcine	Recombinant	1.0×10^{-7}
Canine	LPS-stimulated WB	2.2×10^{-10}
Marmoset	LPS-stimulated PBMC	4.0×10^{-10}
Baboon	Recombinant	6.0×10^{-11}
Chimpanzee	LPS-stimulated PBMC	5.5×10^{-11}
<i>Cynomolgus</i>	LPS-stimulated PBMC	8.0×10^{-11}
Rhesus	LPS-stimulated PBMC	4.0×10^{-11}
Human	Recombinant	1.3×10^{-10}

Neutralization potency for porcine and rabbit TNF was weaker than in human TNF. Adalimumab neutralized murine TNF very weakly, and did not neutralize rat TNF at all. The results demonstrate that monkeys are the most relevant species to human while rodents are not relevant species for assessing the mechanism-based toxicity of adalimumab.

Adalimumab as a human IgG1 antibody exhibits the expected effector functions including Fc receptor binding and complement activation; however, this was found to be of no toxicological relevance.

In contrast to certain murine monoclonal antibodies, adalimumab does not cause the release of cytokines or shedding of cell surface molecules from human peripheral blood cells *ex vivo*.

In vivo testing was limited to human TNF-induced pathologies in animals. Treatment with adalimumab protected mice against TNF lethality in a dose dependent manner. The neutralization potency of adalimumab *in vivo* was further demonstrated by the prevention of TNF-induced pyrexia in rabbits. Adalimumab inhibited the TNF-induced rise in body

temperature in a dose dependent manner. Further, adalimumab administered either alone or in preformed immune complexes with TNF is not pyrogenic in rabbits (**Figure 7**).

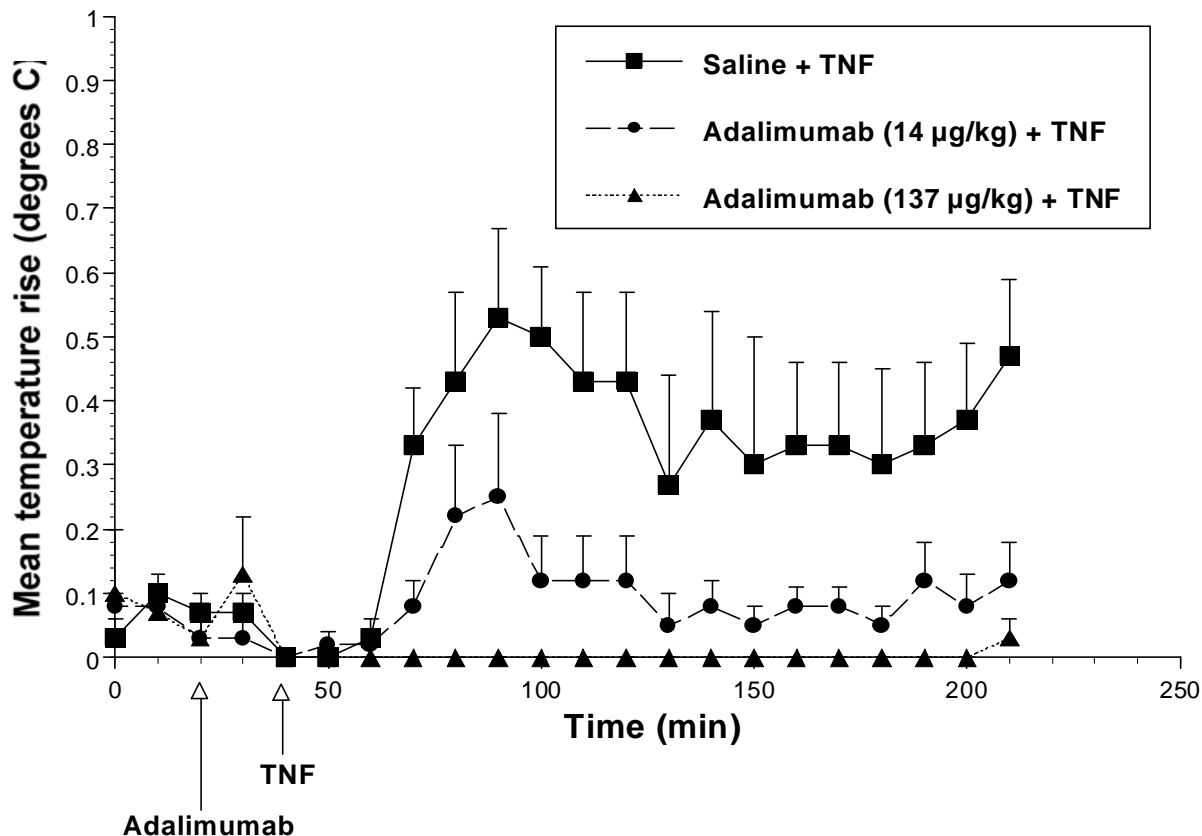


Figure 7. Inhibition of TNF-Induced Pyrexia with Adalimumab in Rabbits
Time 0 refers to the initiation of temperature recordings after the rabbits had settled down in the holding stalls

The prevention of polyarthritis in Tg197 mice carrying the human TNF transgene is an accepted model of rheumatoid arthritis in humans. Joint distortion, swelling, joint deformation, ankylosis and impaired movement were present in untreated, PBS-treated and human IgG1-treated control mice, but were completely absent in mice treated with adalimumab. Similarly, microscopic examinations of mice treated with adalimumab showed no evidence of the synovial thickening, cartilage destruction or bone erosion present in control mice. At lower doses a dose-response relationship of adalimumab to arthritis scores and histology scores was evident. These findings strongly suggest that adalimumab may be an effective therapy for the treatment of rheumatoid arthritis in humans (**Figure 8**).

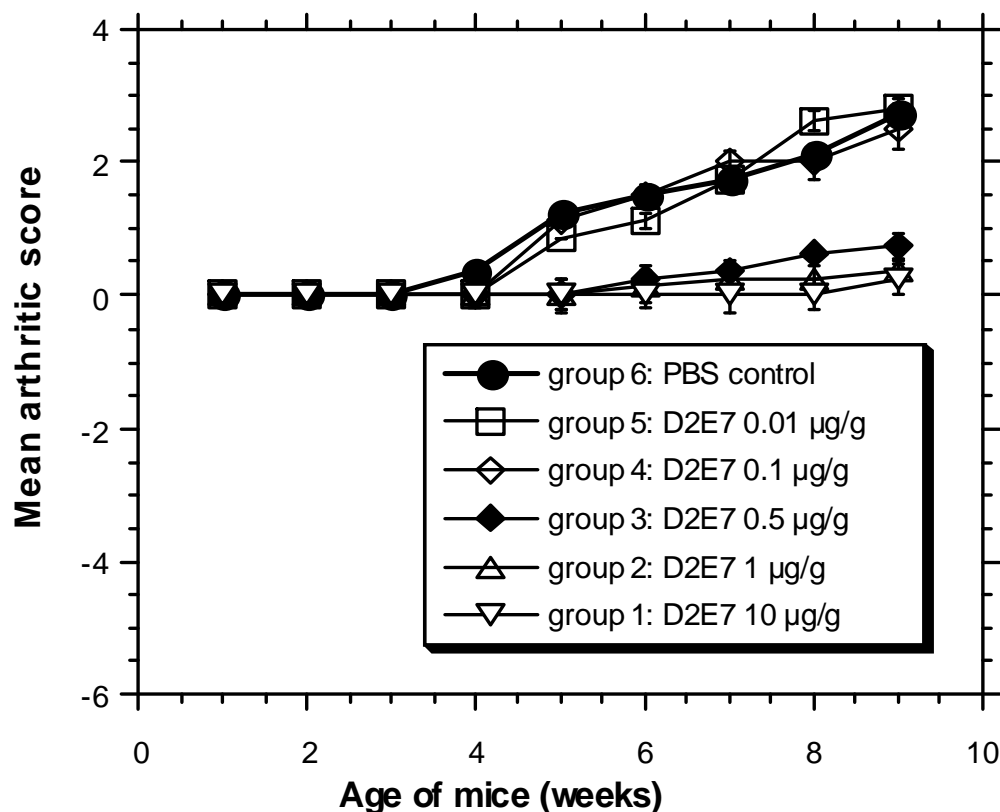


Figure 8. Mean Arthritic Scores of Study Groups During the Study Period
 For each group, average \pm standard error of arthritic score is indicated. Arthritic scores were recorded as follows; 0 = no arthritis, (normal appearance and flexion); 1 = mild arthritis (joint distortion); 2 = moderate arthritis (swelling, joint deformation) and 3 = severe arthritis (ankylosis detected on flexion and severely impaired movement)

In vivo Use of Methotrexate

Methotrexate is widely used in the treatment of patients with rheumatoid arthritis. Adalimumab, either alone or in combination with methotrexate, was effective in preventing the progression of polyarthritis in human TNF transgenic Tg197 mice. In contrast to clinical results, methotrexate was not effective in this model alone and appeared to offer no additional benefit to the adalimumab treatment regimen (**Figure 9**).

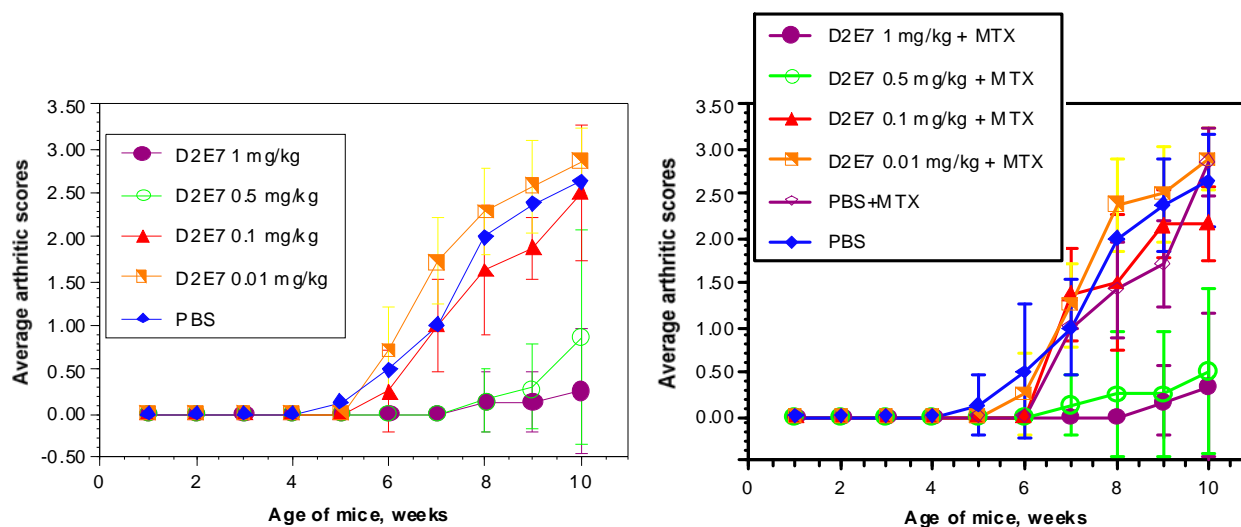


Figure 9. Mean Arthritic Scores of Study Groups During the Study Period
For each group, average \pm standard error of arthritic score is indicated

Pharmacokinetics

All pharmacokinetic evaluations relied on bioanalytical data obtained from two enzyme-linked immunosorbent assay (ELISA) methods that detected only free drug. The fact that both assays required binding to immobilized TNF ensured that only active drug was detected and the requirement to displace the detector-adalimumab or bind a second TNF molecule excluded interference from non-binding antibody fragments. On the other hand, interference from adalimumab:anti-adalimumab antibody complexes was expected, especially when these anti-antibodies are against the idiotype and presumed to be neutralizing.

Free anti-adalimumab antibodies could be directly detected by a sensitive double-antigen ELISA, where these antibodies bridge immobilized capture- and labeled detector-adalimumab. As in the adalimumab ELISA, this assay cannot detect adalimumab:anti-adalimumab antibody complexes either. For the analysis of murine anti-human antibodies (MAHAs) this limitation was overcome by using a sandwich assay, which employed anti-mouse antibodies and detected both free and partly complexed MAHAs. This assay format could not be used for primate anti-human antibody (PAHA) analyses because the anti-monkey IgG detection antibody would have cross-reacted with adalimumab.

The pharmacokinetics of adalimumab were investigated after intravenous and subcutaneous administration, because the pivotal toxicity studies used intravenous administration whereas subcutaneous administration is the intended route in patients. In monkeys, adalimumab was almost completely absorbed after subcutaneous injection. The high bioavailability proved the drug to be suitable for subcutaneous administration (**Figure 10**).

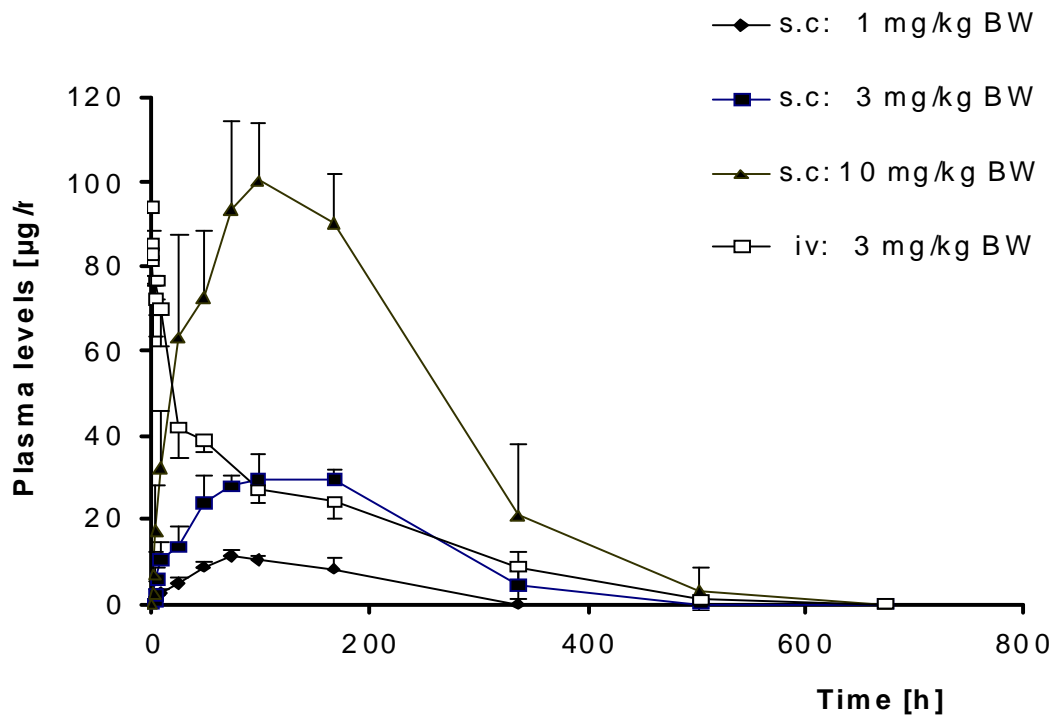


Figure 10. Profiles of Serum Levels After Subcutaneous Administration (mean + SD) of 1, 3 and 10 mg/kg and Intravenous Administration (mean - SD) of 3 mg/kg Body Weight to Male Monkeys

After injection/absorption of adalimumab, serum level-time curves declined in at least two distinct phases. The rather low peripheral apparent volume of distribution suggests that adalimumab may remain in extracellular space.

In both animal species (mice and monkeys), the pharmacokinetics of adalimumab were linear as long as anti-adalimumab antibodies were absent. Area under the curve (AUC) values and maximum serum concentrations increased with dose. Clearance values were dose-independent and pharmacokinetic parameters showed no gender dependency in the relevant monkey test species. Exposure of the animals to adalimumab during the toxicity studies could be demonstrated.

Elimination of adalimumab was slow. Terminal half-lives were 4 to 11 days in mice and 13.5 ± 4.6 days in monkeys in repeat dose studies. The terminal half-life observed in monkeys is similar to the half-life of endogenous IgG in humans.

Administration of adalimumab from several production drug substance batches, produced in different cell lines and with different manufacturing processes had no significant influence on the pharmacokinetic parameters in monkeys. Also, administration of adalimumab in formulations that differed both in concentration of adalimumab and the presence or absence of 0.1% polysorbate 80 had no significant influence on the pharmacokinetic parameters in monkeys.

TOXICOLOGY

Acute Toxicity – Single-Dose Studies

Three single-dose toxicity studies (two in mouse and one in rat) were conducted to obtain the qualitative and quantitative information about the acute toxicity profile of adalimumab after single intravenous administration.

In a mouse study, a single dosage of adalimumab (898 mg/kg) or vehicle control (phosphate buffered saline, PBS) was administered via a tail vein (5/sex/group). The animals were examined for clinical signs for 14 days after treatment. Necropsy was performed 14 days after treatment.

At the highest technically feasible dosage of 898 mg/kg adalimumab based on a 10 mL/kg injection volume and the highest available drug concentration, no deaths occurred. No clinical sign was observed that could be attributed to adalimumab. Body weight gains of the drug-treated mice were comparable to those of the control mice. Pathomorphology did not reveal any toxicologically relevant change. The minimal lethal dosage of adalimumab in mice is greater than 898 mg/kg.

A second single-dose study was done in mice and included an investigation of the formation of MAHAs. Four groups of mice (5/sex/group) were included in this study. The animals were treated intravenously with either a single dosage of vehicle (PBS), or 1.6 mg/kg, 16 mg/kg, or 786 mg/kg of adalimumab (drug substance batch AFP603). Clinical signs, especially the hair coat, were assessed. Blood samples were collected before treatment and at Weeks 3, 5, 7, 9, 11, and 13 after drug administration to determine the adalimumab concentration in serum with an ELISA and to detect MAHA formation with two different ELISA techniques. All animals were sacrificed and subjected to gross examination upon termination of the study. Spleen and skin were evaluated histopathologically.

The general department of the mice and the body weight gains were not affected by treatment with adalimumab. One male at 1.6 mg/kg died on Day 13 during blood sampling under halothane anesthesia. The death of this animal was considered to be associated with the halothane anesthesia and not associated with the adalimumab treatment. Local hair loss in the nasolabial area associated with loss of tactile hairs was observed in all females at 1.6 mg/kg and four out of five females in the control group from Week 5 onwards. The results indicate that the hair loss is not associated with adalimumab treatment since the same effect also was observed in the control mice.

The serum concentration curve of adalimumab was plotted for one mouse from each group. In the control and 1.6 mg/kg groups, the adalimumab serum concentration was always less than 0.6 mcg/mL, whereas at 16 mg/kg group, 70 mcg/mL was found at Week 3. No adalimumab was detected from Week 5 onwards at this dose. At 786 mg/kg group, a concentration as high as 484 mcg/mL was found at Week 3 and a measurable concentration of adalimumab was found up to nine weeks post injection.

The time course of MAHA development also was measured in one mouse from each group. MAHAs were not detected in the control mouse or any pre-treatment sample. Using a double sandwich (double antigen) MAHA assay (called MAHA-1 assay in the report) sensitive to inhibition by adalimumab in the blood, MAHAs were detected as early as Week 5 for the mouse treated at 1.6 mg/kg and not detected until Week 11 for the mouse treated at 16 mg/kg, whereas MAHAs were not detected at any time point for the mouse treated at 786 mg/kg, which was attributed to the assay interference by the high concentrations of circulating adalimumab. Using a direct capture (sandwich) MAHA assay (called MAHA-2 assay in the report) that is less sensitive to adalimumab interference, MAHAs were detected from Week 5 onwards in mice at 1.6 mg/kg and 16 mg/kg and at Weeks 9 and 13 in the 786 mg/kg mouse. Once the kinetics and titers were determined from the sample mouse of each group, MAHAs in all mice treated with adalimumab were analyzed at a dilution of 1:1000 at Week 5 for the 1.6 mg/kg and 16 mg/kg mice, and at Week 13 for the 786 mg/kg mice by the direct capture MAHA assay. MAHAs were detected in all samples, indicating that all the adalimumab-treated mice were MAHA positive after a single intravenous injection.

In the rat single-dose study, a single dosage of adalimumab (898 mg/kg, drug substance batch AF601-Ex pool) or vehicle control (PBS) was administered via a tail vein (5/sex/group). The animals were examined for clinical signs for 14 days after drug administration. Necropsy was performed 14 days after treatment.

At the highest technically feasible dosage of 898 mg/kg adalimumab based on a 10 mL/kg injection volume and the highest available drug concentration, no deaths occurred. Drug-related clinical signs were not observed. Body weight gains of the drug-treated rats were comparable to those of the control rats. Necropsy showed slightly to moderately enlarged spleens in three males at 898 mg/kg, and slightly enlarged spleens in three males in the control group. Histopathology of the enlarged spleens revealed moderate to marked extramedullary hematopoiesis. These changes were not attributed to the drug treatment because they were observed in the control group as well as in the treatment group.

In summary, adalimumab is well tolerated at the highest technically feasible dose and the minimal lethal dose after a single intravenous injection is greater than 898 mg/kg in mice and rats. Adalimumab is immunogenic in mice after a single intravenous dose.

Long-Term Toxicity – Multiple-Dose Studies

Mouse (Four-Week Study)

In a four-week mouse study, the mice were randomly distributed into three study groups. The highest dose in this study provided 16 times the maximum dosage of 10 mg/kg used in early clinical studies.

The mice were intravenously administered either vehicle control (PBS) or adalimumab (drug substance batch AFP603) once per week on days 1, 8, 15, 22, and 29. The main study group was terminated on Day 30 and the recovery study group was allowed to recover for four weeks without further treatment after the last dose. The mice were observed for drug-related clinical

signs at least once daily. Body weight and food consumption was recorded once weekly. Blood samples (0.3 mL) in the main and recovery study groups were collected from the retro-orbital venous plexus under light ether anesthesia on Days 30 and 57 (recovery group only) from mice chosen for hematology, clinical biochemistry and immunogenicity analyses.

There was no clinical sign of toxicity or behavioral changes related to drug treatment. Body weight and body weight gain of drug-treated animals remained in the same range as controls over the treatment and recovery periods.

The results of the toxicokinetic evaluation, using adalimumab level values from pooled serum, revealed that weekly iv administrations of 32, 70.9 and 157.2 mg/kg of adalimumab to mice for four weeks resulted in an increase of serum C_{max} and AUC values (C_{max} : 1193, 1528, 4231 mcg/mL in males, 794, 2069, 5028 mcg/mL in females; AUC: 66782, 104612, 190342 mcg•h/mL in males, 81598, 120693, 240366 mcg•h/mL in females). A slightly lower terminal half-life was observed for male mice than for female mice (97 to 112 hours versus 134 to 259 hours). The AUC values increased in a slightly less than proportional manner and were somewhat higher in female mice. There was, however a high degree of variability in the data.

Significant formation of MAHAs was detected in male and female mice in all drug-treated groups starting on the 8th day after the first administration. The level of MAHAs increased with subsequent doses. Significant differences were observed between 32.0 mg/kg and 70.9 mg/kg dosages ($p < 0.01$) and the 32.0 mg/kg and 157.2 mg/kg dosages ($p < 0.01$), but not between the 70.9 mg/kg and 157.2 mg/kg dosages ($p > 0.05$). This indicates that the MAHAs are detected at all dose levels. Whether the differences between dose levels are due to assay interference or true differences in immunogenicity can not be determined.

Monkey (Four-Week Study)

A four-week study was performed to investigate the potential toxicity of adalimumab in *cynomolgus* monkeys. A total of 32 monkeys (16 males and 16 females) were distributed randomly into four dosage groups, and were administered either the vehicle control (PBS), or adalimumab at 32, 70.9, or 157.2 mg/kg (drug substance batch AFP603) via intravenous injection (*vena saphena magna* of the right or left hind leg). The injections were given once per week on days 1, 8, 15, 22, and 29 for a total of five doses.

The toxicokinetic results showed a dose-proportional increase of serum maximum concentration (C_{max}) of adalimumab and serum AUC. The central volume of distribution ($V_c = \text{dose} / C_{(0)}$) was 39.7 ± 7.9 mL/kg (mean \pm standard deviation). The AUCs corresponding to single-dose amounts of 32, 70.9, and 157.2 mg/kg, were 201317 ± 88835 , 359667 ± 127283 and 808900 ± 200581 mcg•h/mL, respectively. The terminal half-life was 13.5 ± 4.6 days and the clearance was 0.20 ± 0.07 mL/h/kg. No sex dependency of pharmacokinetic parameters and no influence of dose on total clearance were noted.

Immunohistochemistry data showed a minimal decrease of CD21⁺ B-cells in the spleen follicles of the male monkeys treated with 70.9 and 157.2 mg/kg.) A reduced cytoplasmic immunostaining of IgG and IgM was also observed in the germinal centers of the follicles in

most treated monkeys at all doses. No such change was observed in the follicles in the lymph nodes. All these changes were very subtle and generally reversible. Therefore, these changes were considered to be the result of pharmacologically functional effects of adalimumab rather than toxicological effects. No deposits of immune-complexes were found in kidney, lung, liver, skin, spleen, thymus, lymph nodes, skeletal muscle, and heart.

Monkey (39-Week Study)

A 39-week study in *cynomolgus* monkeys was done to evaluate the potential toxicity and reversibility of any toxic effect of adalimumab. A total of 32 animals (16 males and 16 females) were randomly distributed into four groups, and were administered either vehicle control (PBS buffer) or adalimumab at 32, 82.9, or 214.8 mg/kg. The test article or control agent was administered by intravenous injection into a vena saphena magna, once per week for 39 weeks (total of 40 injections).

There were no significant differences in clinical signs of toxicity or behavior and food consumption over the treatment and recovery periods in the drug-treated groups as compared to the control animals. Body weights of the animals treated with 32 and 82.9 mg/kg were not affected as compared with the control animals. In the 214.8 mg/kg group, a slight, transient decrease in the body weight was observed in test Week 4, and completely recovered from test Week 6 onwards. The body weights of the female animals in this group were decreased slightly from test Week 2 onwards. The decreases were not statistically significant at $p \leq 0.01$ as compared with the control animals and were within the normal fluctuation of body weight.

The examination of immune complexes showed a reduced antigen expression of IgG and IgM in the follicular dendritic cells of the spleen in all drug-treated monkeys. Concomitantly, the follicular dendritic cells were reduced in number and the normally dense network was altered. In parallel, the IgG or IgM positive plasma cell count increased slightly in the spleen independently of the different compartments. These changes were considered to be the pharmacologically functional effects of adalimumab rather than toxicological effects.

Toxicokinetic results reported in Report No. MPF/EBB 9741 showed an increase of steady-state serum concentrations and AUC values. At dosages of 32, 82.9, and 214.8 mg/kg of adalimumab, the corresponding C_{max} (mean \pm standard deviation) at five minutes after the last administration were 2731 ± 467 , 6527 ± 2450 , 13563 ± 1740 mcg/mL and the corresponding serum AUCs were 304774 ± 74634 , 617368 ± 233959 , and 1299965 ± 228114 mcg•h/mL, respectively. The corresponding clearances were 0.11 ± 0.04 , 0.16 ± 0.07 , and 0.17 ± 0.03 mL/h/kg, respectively. The terminal half-life, evaluated from data obtained during the recovery phase of two male and two female monkeys, was 16.2 ± 3.4 days. No sex dependency of pharmacokinetic parameters and no influence of dose on the clearance were noted.

The distribution of adalimumab in the vascular compartment was broad in the lungs, liver, and skin at 214.8 mg/kg. Cartilage staining in the bronchi with anti-adalimumab antibodies was observed in several treated monkeys at 32 mg/kg onwards. In the synovial membrane, adalimumab was detected in the vascular compartment mainly at 214.8 mg/kg, and additionally in one male monkey at 82.9 mg/kg.

Most of the immunohistochemical changes observed in kidneys, spleen, and lungs were found to be reversible. However, the cellular diminution in the thymus in males was partially reversed, and did not reach the cellularity of the control animals after a 20-week recovery period. No adalimumab could be detected after the 20-week recovery period in the vessels of the organs and tissues examined.

Mutagenicity and Carcinogenicity

No carcinogenicity study was performed for adalimumab.

In vitro Genotoxicity

The mutagenic potential of adalimumab was tested in the Ames test and in the *Escherichia coli* reverse mutation assay. These tests are based on the ability of the test article to induce reverse mutations in selected loci of bacteria. *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537, as well as *Escherichia coli* strain WP2 uvrA were used. Adalimumab (drug substance batch AF601-Ex pool) was tested at concentrations of 0, 20, 100, 500, 2500 and 5000 mcg/plate. Three plates were used per dose. Positive controls and a vehicle control (PBS buffer) were included in each experiment. Both the standard plate test (Ames test) and preincubation test with and without the addition of an exogenous metabolic activation system (S-9 fraction prepared from the livers of Aroclor 1254 treated rats) were performed. The results were considered positive if the revertant rate of a treatment group was at least twice that of the spontaneous revertant rate (vehicle control), a dose-response relationship occurred, and the experiments were reproducible.

No bacteriotoxic effect, such as reduced His⁻ or Trp⁻ background growth and decreased number of His⁺ or Trp⁺ revertants, were observed in adalimumab-treated plates when compared to the vehicle control. There was no increase in the number of mutant colonies under any experimental conditions in any strain of bacteria for the test article, whereas the positive controls showed the expected response when compared to the vehicle control. Therefore, the test substance is not mutagenic either in the Ames test or in the *E. coli* reverse mutation assays.

In vivo Genotoxicity

The potential clastogenic and spindle poison effects of adalimumab were tested in an in vivo micronucleus assay in NMRI mice after a single intravenous dose. The mice were randomly allocated into eight groups: two vehicle control groups (five mice/sex/group), four treatment groups (five mice/sex/group), and two positive control groups (five mice/group). The mice were intravenously treated once either with the vehicle control (PBS buffer); 224.5, 449.0, or 898 mg/kg (two groups) of adalimumab (drug substance batch AF601-Ex pool); or positive controls of 20 mg cyclophosphamide (two male and three female) or 0.15 mg/kg vincristine (three male and two female). All animals were sacrificed 24 hours after treatment except for one vehicle control group and one 898 mg/kg group, which were sacrificed 48 hours after dosing.

Bone marrow slides were prepared and stained with eosin and methylene solution, followed by Giemsa stain. The slides were examined microscopically for the following parameters: number of polychromatic erythrocytes (PCE), number of PCE containing micronuclei (MN), number of normochromatic erythrocytes (NCE), number of NCE containing MN, number of small micronuclei, and number of large micronuclei. The ratio of PCE to NCE was calculated. The results were considered positive if the following criteria were met: a dose-related and significant increase in the number of micronucleated PCE at the 24-hour and/or 48-hour intervals, and the proportion of cells containing micronuclei exceeded both the values of the concurrent negative control range and the negative historical control range.

The number of PCE and NCE containing MN in the adalimumab-treated groups was not significantly different from the concurrent, negative controls at any of the sacrificed intervals. However, the percentage of small MN in PCE in the cyclophosphamide-treated group and the percentage of large MN in PCE in the vincristine-treated group increased significantly as compared with the vehicle control. The ratio of PCE to NCE in all dose groups was always in the same range as that of the control values, suggesting normal erythropoiesis.

The results indicate that adalimumab does not have clastogenic activity or spindle poison effects. Also, no inhibition of erythropoiesis induced by the treatment with adalimumab was observed in NMRI mice.

Reproduction and Teratology

In pregnant monkeys adalimumab was distributed into the serum of the fetus and into the amnion fluid showing a distribution pattern that would be expected of a human IgG in a pregnant woman. No drug-related toxicity was observed. Distribution of adalimumab into the milk was not determined.

REFERENCES

1. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatology Association 1987 Revised Criteria for the Classification of Rheumatoid Arthritis. *Arthritis Rheum* 1988; 31:315-24.
2. Baecklund E, Ekbom A, Sparén, et al. Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case-control study. *BMJ* 1998; 317:180-181.
3. Canadian Tuberculosis Standards. 5th Edition. 2000. Joint production of the Canadian Lung Association/Canadian Thoracic Society and Tuberculosis and Control, Centre for Infectious Disease Prevention and Control, Health Canada.
4. Centers for Disease Control and Prevention. Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection. *MMWR* 2000; 49(No. RR-6):26-38.
5. Mellekjaer L, Linet MS, Gridley G, et al. Rheumatoid arthritis and cancer risk. Original Paper. *Eur. J Cancer* 1996; 32A(10):1753-1757.
6. Ramey DR, Fries JF, Singh G. The Health Assessment Questionnaire 1995 - Status and Review. In: Spilker B, ed. "Quality of Life and Pharmacoeconomics in Clinical Trials." 2nd ed. Philadelphia, PA. Lippincott-Raven 1996.
7. Waldmann TA, Strober W. Metabolism of Immunoglobulins. *Progr Allergy* 1969; 13:1-110.
8. Ware JE, Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. *J Clin Epidemiol* 1998; 51(11):903-12.

PART III: CONSUMER INFORMATION

PrHUMIRA[®] subcutaneous injection adalimumab

This leaflet is PART III of a three-part “Product Monograph” published when HUMIRA[®] (Hu-MARE-ah) was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about HUMIRA[®]. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

HUMIRA[®] treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn’s disease (CD), or psoriasis (Ps), and familiar with the HUMIRA[®] efficacy and safety profile.

What the medication is used for:

HUMIRA[®] is a medicine that is used in people with moderate to severe rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn’s disease, or psoriasis.

- Rheumatoid arthritis is an inflammatory disease of the joints.
- Psoriatic arthritis is an inflammatory disease of the joints and skin.
- Ankylosing spondylitis is a form of arthritis.
- Crohn’s disease is an inflammatory disease of the digestive tract.
- Psoriasis is an inflammatory disease of the skin. Your doctor prescribed HUMIRA[®] to reduce the signs and symptoms of your plaque psoriasis.

People with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, or psoriasis may be given other medicines for their disease before they are given HUMIRA[®]. If you have Crohn’s disease, you will first be given other medicines. If you do not respond well enough to these medicines, you will be given HUMIRA[®] to reduce the signs and symptoms of your disease.

What it does:

HUMIRA[®] is a fully human monoclonal antibody produced by cultured cells. Monoclonal antibodies are proteins that recognize and bind to other unique proteins. HUMIRA[®] binds to a specific protein called TNF-alpha (also known as tumor necrosis factor). People with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn’s disease, or psoriasis have too much of TNF-alpha in their bodies. The extra TNF-alpha in your body can attack normal healthy body tissues and cause inflammation, especially in the tissues of your bones, cartilage, joints and digestive tract. By

binding to TNF-alpha, HUMIRA[®] decreases the inflammation process of these diseases.

HUMIRA[®] helps reduce the signs and symptoms of rheumatoid arthritis and psoriatic arthritis (such as pain and swollen joints), may help improve your ability to perform daily activities (such as getting dressed, walking and climbing stairs), and may help prevent further damage to your bones and joints. In addition, HUMIRA[®] helps reduce the signs and symptoms of ankylosing spondylitis (back pain and morning stiffness), and Crohn’s disease (abdominal pain and diarrhea). HUMIRA[®] also helps reduce the signs and symptoms of psoriasis (such as pain, itching and scaly patches on skin). HUMIRA[®], however can also lower your body’s ability to fight infections. Taking HUMIRA[®] can make you more prone to getting infections or make any infection you have worse.

When it should not be used:

You should not take HUMIRA[®] if you have:

- an allergy to any of the ingredients in HUMIRA[®] (see **What the important non-medicinal ingredients are** section). The needle cover of the syringe contains dry natural rubber (latex). Tell your doctor if you have any allergies to rubber or latex.
- a serious infection such as tuberculosis, infections caused by bacteria or fungi, and bacterial infections that have spread throughout the body (sepsis).

What the medicinal ingredient is:

adalimumab

What the important non-medicinal ingredients are:

citric acid monohydrate, dibasic sodium phosphate dihydrate, mannitol, monobasic sodium phosphate dihydrate, polysorbate 80, sodium citrate, sodium chloride

For a full listing of non-medicinal ingredients see PART I of the Product Monograph.

What dosage forms it comes in:

- Single-use, 1 mL pre-filled Pen containing 40 mg adalimumab dissolved in 0.8 mL sterile solution (50 mg/mL)
- Single-use, 1 mL pre-filled glass syringe containing 40 mg adalimumab dissolved in 0.8 mL sterile solution (50 mg/mL)

WARNINGS AND PRECAUTIONS

Before initiation, during and after treatment with HUMIRA[®], you should be evaluated for active or latent tuberculosis infection with a tuberculin skin test.

Any medicine can have side effects. Like all medicines that affect your immune system, HUMIRA[®] can cause serious side effects. The possible serious side effects include:

Serious Warnings and Precautions

- **Allergic reactions:** If you develop a severe rash, swollen face or difficulty breathing while taking HUMIRA[®], call your doctor right away.
- **Hepatosplenic T-cell lymphoma:** Very rare post-marketing reports of hepatosplenic T-cell lymphoma (HSTCL), a rare aggressive lymphoma that is often fatal, have been identified in patients treated with HUMIRA[®]. Most of the patients had prior infliximab therapy as well as concomitant azathioprine or 6-mercaptopurine used for Crohn's disease. The causal association of HSTCL with HUMIRA[®] is not clear.
- **Lupus-like symptoms:** Some patients have developed lupus-like symptoms that got better after their treatment was stopped. If you have chest pains that do not go away, shortness of breath, joint pain or a rash on your cheeks or arms that is sensitive to the sun, call your doctor right away. Your doctor may decide to stop your treatment.
- **Malignancies:** There have been very rare cases of certain kinds of cancer in patients taking HUMIRA[®] or other TNF-blockers. Some patients receiving HUMIRA[®] have developed types of cancer called non-melanoma skin cancer. Tell your doctor if you have a bump or open sore that does not heal. People with more serious rheumatoid arthritis that have had the disease for a long time may have a higher than average risk of getting a kind of cancer that affects the lymph system, called lymphoma. If you take HUMIRA[®] or other TNF-blockers, your risk may increase.
- **Nervous system diseases:** There have been rare cases of disorders that affect the nervous system of people taking HUMIRA[®] or other TNF-blockers. Signs that you could be experiencing a problem affecting your nervous system include: numbness or tingling, problems with your vision, weakness in your legs, and dizziness.
- **Pediatric Cancer:** Lymphoma and other cancers, which may result in death, have been reported in children and teenage patients taking TNF-blockers, including HUMIRA[®].
- **Serious infections:** There have been rare cases where patients taking HUMIRA[®] or other TNF-blocking agents have developed serious infections. Some of these cases have been life-threatening. Such infections include tuberculosis, infections caused by bacteria or fungi, bacterial infections that have spread throughout the body (sepsis), and very rare cases of hepatitis B infection relapse.

- **Blood Problems:** In some instances, patients treated with TNF-blocking agents may develop low blood counts. If you develop symptoms such as persistent fever, bleeding, or bruising, you should contact your doctor right away.
- **Pediatric Cancer:** There have been cases of cancers, including unusual types, in children and teenage patients taking TNF-blocking agents, which sometimes resulted in death. For children and adults taking TNF-blocker medicines, the chances of developing lymphoma or other cancers may increase.

BEFORE you start taking HUMIRA[®], you should tell your doctor if you have or have had any of the following:

- any kind of infection including an infection that is in only one place in your body (such as an open cut or sore), or an infection that is in your whole body (such as the flu). Having an infection could put you at risk for serious side effects from HUMIRA[®]. If you are unsure, ask your doctor.
- a history of infections that keep coming back or other conditions that might increase your risk of infections, including fungal infections.
- if you have ever had tuberculosis, or if you have been in close contact with someone who has had tuberculosis. If you develop any of the symptoms of tuberculosis (a dry cough that doesn't go away, weight loss, fever, night sweats) call your doctor right away. Your doctor will need to examine you for tuberculosis and perform a skin test.
- if you resided or traveled to areas where there is a greater risk for certain kinds of infections such as tuberculosis, histoplasmosis, coccidioidomycosis, blastomycosis, or parasitic infections. These infections are caused by a bacteria or a fungus that can affect the lungs or other parts of your body. If you take HUMIRA[®] these may become active or more severe. If you don't know if you have lived in an area where these infections are common, ask your doctor.
- if you have ever had hepatitis B virus infection or are at risk of developing this infection. Signs and symptoms of hepatitis B virus infection include the following: yellowing of the skin or eyes (jaundice), feeling of sickness, tiredness, loss of appetite, joint pain, and abdominal pain. If you experience any of these signs and symptoms, contact your doctor immediately. These symptoms may occur several months after starting therapy with HUMIRA[®].
- if you experience any numbness or tingling or have ever had a disease that affects your nervous system like multiple sclerosis.
- if you are scheduled to have major surgery.
- if you are scheduled to be vaccinated for anything.

- you are taking other medicines for your rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn’s disease, psoriasis, or other conditions. You can take other medicines provided your doctor has prescribed them, or has told you it is ok to take them while you are taking HUMIRA®. It is important that you tell your doctor about any other medicines you are taking for other conditions (for example, high blood pressure medicine) before you start taking HUMIRA®.
- you are taking any over-the-counter drugs, herbal medicines and vitamin and mineral supplements.
- you are pregnant, thinking of becoming pregnant, or are breast-feeding. HUMIRA® has not been studied in pregnant women or nursing mothers, so the effects on pregnant women or nursing babies are unknown.

If you are not sure or have any questions about any of this information, ask your doctor.

INTERACTIONS WITH THIS MEDICATION

You should not take HUMIRA® with:

- other TNF-blockers
- abatacept (Orencia®)
- anakinra (Kineret®)

If you have questions, ask your doctor.

PROPER USE OF THIS MEDICATION

Usual Dose:

Adults with Rheumatoid Arthritis, Psoriatic Arthritis or Ankylosing Spondylitis:

- The recommended dose is 40 mg administered every other week as a subcutaneous injection.

Adults with Crohn’s Disease:

- The recommended induction dose is 160 mg at Week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days), followed by 80 mg at Week 2.
- The recommended maintenance dose regimen is 40 mg every other week beginning at Week 4.

Adults with Psoriasis:

- The recommended dose is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose.

Overdose:

If you accidentally inject HUMIRA® more frequently than instructed, contact your doctor or local poison control center right away.

Missed Dose:

If you forget to give yourself an injection, you should inject the missed dose of HUMIRA® as soon as you remember. Then take your next dose as you would have on your originally scheduled date.

Administration:

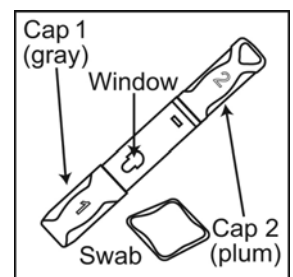
The following instructions explain how to inject HUMIRA®. Please read the instructions carefully and follow them step-by-step. You will be instructed by your doctor or his/her assistant on the technique of self-injection. Do not attempt to self-inject until you are sure that you understand how to prepare and give the injection. After proper training, the injection can be self-administered or given by another person; for example, a family member or friend.

This injection should not be mixed in the same syringe with any other medicine.

Step 1. Setting Up

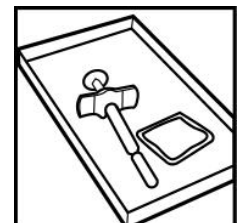
- Remove one dose tray containing a HUMIRA® Pen or pre-filled syringe from the refrigerator.
 - Do not shake or drop the Pen or pre-filled syringe.
 - Do not use the Pen or pre-filled syringe if it is frozen or if it has been left in direct sunlight.
 - If you are using the Pen, only remove the caps **immediately** before injection.
- Set up the following on a clean, flat working surface:

- One HUMIRA® Pen
- One alcohol pad (swab)



-OR-

- One pre-filled syringe of HUMIRA® for injection
- One alcohol pad (swab)

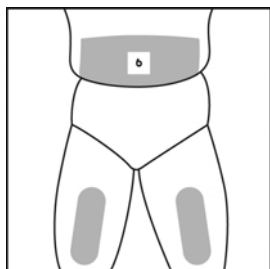


- If you do not have all of the pieces you need to give yourself an injection, call your pharmacist. Use only the items provided in the box your HUMIRA® prescription comes in.
- Make sure that the name HUMIRA® appears on the dose tray and Pen or pre-filled syringe label.
- Check the expiry date on the Pen or pre-filled syringe. Do not use the product if the date has passed the month and year shown.
- Make sure the liquid in the Pen or pre-filled syringe is clear and colourless. Do not use the Pen or pre-filled syringe if the liquid is cloudy or discoloured or if flakes or particles can be seen.
- Have a puncture-proof container nearby for disposing of the used Pen, needles and syringe.

FOR YOUR PROTECTION, IT IS IMPORTANT THAT YOU FOLLOW THESE INSTRUCTIONS.

Step 2. Choosing and Preparing The Injection Site

- Wash your hands thoroughly
- Choose a site on the front of your thighs or your abdomen. If you choose your abdomen, you should avoid the area 2 inches around your navel.
- Choose a different site each time you give yourself an injection. Each new injection should be given at least one inch from a site you used before. Do **NOT** inject into areas where the skin is tender, bruised, red or hard or where you have scars or stretch marks.
- You may find it helpful to keep notes on the location of previous injections.

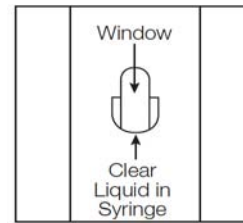


- Wipe the injection site where HUMIRA® is to be injected with an alcohol pad (swab), using a circular motion. Do **NOT** touch this area again before giving the injection.

Step 3. Preparing The Dose for Injection

HUMIRA® Pen

- Hold the Pen with the gray cap pointing up. Check the appearance of the solution through the windows on the sides of the Pen to make sure the liquid is clear and colourless. Do not use the Pen if the liquid is cloudy or discoloured or has flakes or particles in it. Do not use if frozen or if it has been left in direct sunlight.



HUMIRA® Pre-Filled Syringe

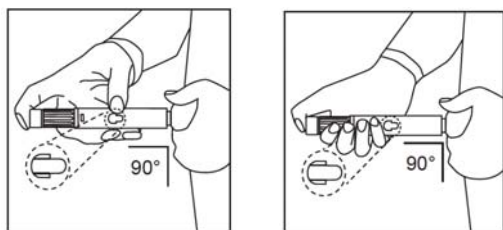
- Remove the needle cover from the syringe, taking care not to touch the needle with your fingers or allowing it to touch any surface.
- Turn the syringe so the needle is facing up and slowly push the plunger in to push the air in the syringe out through the needle. If a small drop of liquid comes out of the needle, this is acceptable.

Step 4. Injecting HUMIRA®

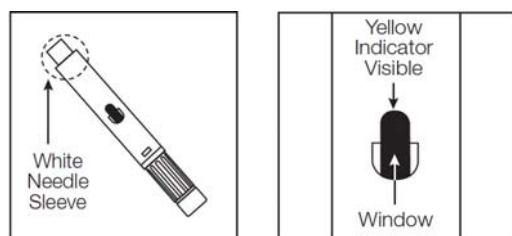
HUMIRA® Pen

- Only remove the caps **immediately** before injection.
- Hold the gray body of the Pen with one hand.
 - Place your hand on the middle of the Pen so that neither the gray cap (Cap 1) nor the plum cap (Cap 2) is covered.
 - Hold the Pen with the gray cap (Cap 1) pointing up.
- With your other hand, pull the gray cap (Cap 1) straight off (without twisting) and discard the cap.
 - Check that the small gray needle cover of the syringe has been removed with the cap.
 - If a few small drops of liquid come out of the needle, this is okay.
 - The white needle sleeve, which covers the needle, will now be exposed. Do not try to touch the needle housed in the barrel.
 - **DO NOT RECAP as you may damage the needle.**
 - Care should be taken to avoid dropping or crushing the product as it contains a glass syringe.
- Pull the plum safety cap (Cap 2) straight off (without twisting) to expose the plum-coloured activation button. The Pen is now ready to use.
 - Please note that the Pen is activated after removing Cap 2 and that pressing the button under Cap 2 will immediately result in discharge of medication.
 - Do not press the plum-coloured activation button until properly positioned.
 - **DO NOT RECAP as this could cause the unit to discharge.**
- Hold the Pen so that the window is in view. The presence of one or more bubbles in the window is normal.
- With your free hand, gently squeeze a sizable area of the cleaned skin at the injection site and hold firmly. You will inject into this raised area of skin.

- Place the white end of the Pen straight (a 90° angle) and flat against the raised area of skin. Position the Pen so that it will not inject the needle into your fingers.
- With your index finger or thumb, press the plum-coloured button to begin the injection.
 - Try not to cover the window.
 - Note that you will hear a loud ‘click’ when you press the button, which indicates the start of the injection. You will feel a small prick as the needle advances.
 - Keep pressing and continue to hold the Pen with steady pressure in place for about **10 seconds to ensure complete injection**. (A way to remember is simply ‘click and count to 10’.) Do not remove the Pen while the injection is being given.
 - It is important to maintain steady pressure at the injection site for the entire period of time.



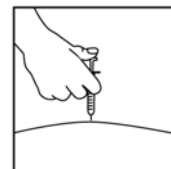
- You will see a yellow indicator move into the windows during the injection. The injection is complete when the yellow indicator stops moving.
- Lift the Pen straight up from the injection site. The white needle sleeve will move down over the needle and lock into place over the needle tip. Do not try to touch the needle. The white needle sleeve is there to protect you from touching the needle.



- Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. Do **NOT** rub the injection site. If you have slight bleeding, this is normal.
- Dispose of the Pen immediately into your special sharps container.

HUMIRA® Pre-Filled Syringe

- With one hand, gently pinch the cleaned area of skin and hold it firmly. With the other hand, hold the syringe like a pencil at about a 90° angle to the skin.



- With a quick, short, “dart-like” motion, push the needle into the skin.
- After the needle is in, let go of the skin. If blood appears in the syringe, it means that you have entered a blood vessel. Do not inject HUMIRA®. Withdraw the needle and repeat the steps to choose and clean a new injection site, however do **NOT** use the same syringe (discard the syringe in your puncture-proof container). If no blood appears, slowly push the plunger all the way in until all of the HUMIRA® is injected.
- When the syringe is empty, remove the needle from the skin, being careful to keep it at the same angle as it was when it was inserted.
- Immediately press a cotton ball or gauze pad over the injection site and hold for 10 seconds. Slight bleeding may occur. Do **NOT** rub the injection site. A bandage is optional.
- Dispose of the syringe immediately into your special sharps container.

Step 5. Disposing of Supplies

- You should always check with your healthcare provider (e.g., doctor, nurse, or pharmacist) for instructions on how to properly dispose of used needles and syringes (including the Pen). Do **NOT** use the same needle and syringe more than once. You should follow any special provincial or local laws regarding the proper disposal of needles and syringes. **Do NOT throw used needles or syringes (including the Pen) in the household trash or recycling bin.**
- Dispose of used needles and syringes (including the Pen) in a container made specially for this purpose (“Sharps” container), or a hard plastic container with a screw-on cap or metal container with a plastic lid labelled “Used Syringes”. Do not use glass or clear plastic containers.
- Always keep the container out of the reach of children.
- When the container is about two-thirds full, tape the cap or lid down so it does not come off and dispose of it as instructed by your doctor, nurse or pharmacist. **DO NOT THROW THE CONTAINER IN THE HOUSEHOLD TRASH OR RECYCLING BIN.**

- The used alcohol pads may be placed in the trash, unless otherwise instructed by your doctor, nurse or pharmacist. The dose tray and cover may be recycled.



SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, HUMIRA® can cause side effects. Most side effects are mild to moderate. However, some may be serious and require treatment.

Tell your doctor immediately if you experience any of the following:

- severe rash, hives or other signs of allergic reaction
- swollen face, hands, feet
- trouble breathing, swallowing
- sudden weight gain (this is possibly indicative of new or worsening heart failure)
- bruising or bleeding very easily, looking very pale (this is possibly indicative of a blood problem)

Tell your doctor as soon as possible if you experience any of the following:

- signs of infection such as fever, malaise, wounds, dental problems, burning on urination
- feeling weak or tired
- coughing
- tingling
- numbness
- double vision
- arm or leg weakness
- bump or open sore that does not heal
- red scaly patches or raised bumps that are filled with pus (this is possibly indicative of new or worsening psoriasis or infection)
- alopecia (loss of hair)
- changes in the pigmentation of the skin
- worsening of the appearance of a scar
- night sweats
- weight loss

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Common	Injection site reaction		✓	
Common	Upper respiratory tract infections		✓	
	Headache	✓		
	Rash		✓	
	Nausea		✓	
Uncommon	Tuberculosis		✓	✓
	Other serious infections		✓	✓
	Nerve disorder		✓	✓

This is not a complete list of side effects. For any unexpected effects while taking HUMIRA®, contact your doctor or pharmacist.

HOW TO STORE IT

Keep HUMIRA® and all other medicines out of the reach of children.

Store between 2 and 8°C (in a refrigerator) in the original container until ready to use. **DO NOT FREEZE HUMIRA®.** Protect from light. Refrigerated HUMIRA® remains stable until the expiration date printed on the Pen or pre-filled syringe. Do not use beyond the expiration date.

Care should be taken to avoid dropping or crushing the product as it contains a glass syringe.

General Advice About Prescription Medicines

Talk to your doctor or other health care provider if you have any questions about this medicine or your condition. Medicines are sometimes prescribed for purposes other than those listed in a **CONSUMER INFORMATION** leaflet. If you have any concerns about this medicine, ask your doctor. Your doctor or pharmacist can give you information about this medicine that was written for health care professionals. Do not use this medicine for a condition for which it was not prescribed. Do not share this medicine with other people. A toll-free information service is also available at 1-866-8HUMIRA (1-866-848-6472).

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report on line at:
www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701C
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at <http://www.healthcanada.gc.ca/medeffect>

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at:

<http://www.abbott.ca>

or by contacting the sponsor, Abbott Laboratories, Limited, Saint-Laurent, Qc H4S 1Z1 at:
1-866-8HUMIRA (1-866-848-6472)

This leaflet was prepared by Abbott Laboratories, Limited.

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