HUMIRA®
(adalimumab)

WARNING

RISK OF INFECTIONS

TUBERCULOSIS (FREQUENTLY DISSEMINATED OR EXTRAPULMONARY AT CLINICAL PRESENTATION), INVASIVE FUNGAL INFECTIONS, AND OTHER OPPORTUNISTIC INFECTIONS, HAVE BEEN OBSERVED IN PATIENTS RECEIVING HUMIRA. SOME OF THESE INFECTIONS HAVE BEEN FATAL (SEE WARNINGS). ANTI-TUBERCULOSIS TREATMENT OF PATIENTS WITH LATENT TUBERCULOSIS INFECTION REDUCES THE RISK OF REACTIVATION IN PATIENTS RECEIVING TREATMENT WITH HUMIRA. HOWEVER, ACTIVE TUBERCULOSIS HAS DEVELOPED IN PATIENTS RECEIVING HUMIRA WHOSE SCREENING FOR LATENT TUBERCULOSIS INFECTION WAS NEGATIVE.

PATIENTS SHOULD BE EVALUATED FOR LATENT TUBERCULOSIS INFECTION WITH A TUBERCULIN SKIN TEST. TREATMENT OF LATENT TUBERCULOSIS INFECTION SHOULD BE INITIATED PRIOR TO THERAPY WITH HUMIRA. PHYSICIANS SHOULD MONITOR PATIENTS RECEIVING HUMIRA FOR SIGNS AND SYMPTOMS OF ACTIVE TUBERCULOSIS, INCLUDING PATIENTS WHO ARE TUBERCULIN SKIN TEST NEGATIVE.

DESCRIPTION

	Proprietary name:		HUMIRA
	Established name:		adalimumab
	Route of administration:		SUBCUTANEOUS (C38299)
	Active ingredients (moiety):		adalimumab (adalimumab)
#	**Strength**	**Form**	**Inactive ingredients**
1	40 MILLIGRAM	INJECTION, SOLUTION (C42945)	sodium chloride, monobasic sodium phosphate dihydrate, dibasic sodium phosphate dihydrate, sodium citrate, citric acid monohydrate, mannitol, polysorbate 80, Water for Injection, Sodium hydroxide
2	40 MILLIGRAM	INJECTION, SOLUTION (C42945)	sodium chloride, monobasic sodium phosphate dihydrate, dibasic sodium phosphate dihydrate, sodium citrate, citric acid monohydrate, mannitol, polysorbate 80, Water for Injection, Sodium hydroxide

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

HUMIRA is supplied as a sterile, preservative-free solution of adalimumab for subcutaneous administration. The drug product is supplied as either a single-use, 1 mL prefilled glass syringe or as a single-use, prefilled pen (HUMIRA Pen). Enclosed within the pen is a single-use, 1 mL prefilled glass syringe. The solution of HUMIRA is clear and colorless, with a pH of about 5.2. Each syringe delivers 0.8 mL (40 mg) of drug product. Each 0.8 mL of HUMIRA contains 40 mg adalimumab, 4.93 mg sodium chloride, 0.69 mg monobasic sodium phosphate dihydrate, 1.22 mg dibasic sodium phosphate dihydrate, 0.24 mg sodium citrate, 1.04 mg citric acid monohydrate, 9.6 mg mannitol, 0.8 mg polysorbate 80 and Water for Injection, USP. Sodium hydroxide added as necessary to adjust pH.

CLINICAL PHARMACOLOGY

General

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

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

Pharmacodynamics

After treatment with HUMIRA, 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. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodeling responsible for cartilage destruction were also decreased after HUMIRA administration.

Pharmacokinetics

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

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

Adalimumab mean steady-state trough concentrations of approximately 5 µg/mL and 8 to 9 µg/mL, were observed without and with methotrexate (MTX) respectively. 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 revealed that there was a trend toward higher apparent clearance of adalimumab in the presence of anti-adalimumab antibodies, and lower clearance with increasing age in patients aged 40 to > 75 years.

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

The pharmacokinetics of adalimumab in patients with AS and RA were similar.

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

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

HUMIRA has not been studied in children.

Drug Interactions

MTX reduced adalimumab apparent clearance after single and multiple dosing by 29% and 44% respectively.

CLINICAL STUDIES

Rheumatoid Arthritis

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

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

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

Study III evaluated 619 patients who had an inadequate response to MTX. Patients received placebo, 40 mg of HUMIRA every other week with placebo injections on alternate weeks, or 20 mg of HUMIRA weekly for up to 52 weeks. Study III had an additional primary endpoint at 52 weeks of inhibition of disease progression (as detected by X-ray results). Upon completion of the first 52 weeks, 457 patients enrolled in an open-label extension phase in which 40 mg of HUMIRA was administered every other week for up to 104 weeks.

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

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

Clinical Response

The percent of HUMIRA treated patients achieving ACR 20, 50 and 70 responses in Studies II and III are shown in Table 1.

Table 1. ACR Responses in Studies II and III (Percent of Patients)

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

* $p < 0.01$, HUMIRA vs. placebo

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

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

Table 2. Components of ACR Response in Studies II and III

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

a 40 mg HUMIRA administered every other week

b Visual analogue scale; 0 = best, 10 = worst

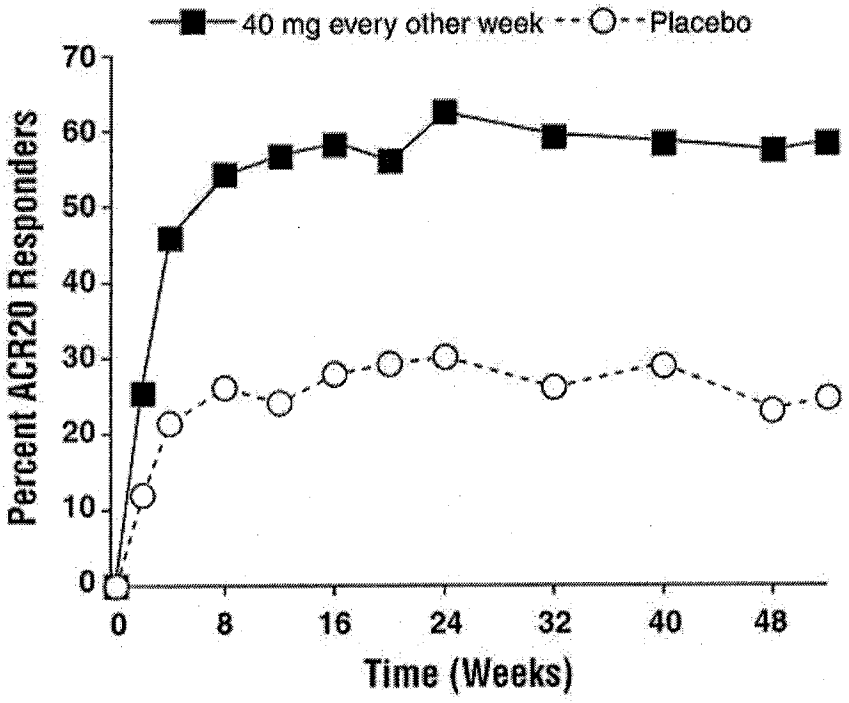
c Disability Index of the Health Assessment Questionnaire[2]; 0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity

* $p < 0.001$, HUMIRA vs. placebo, based on mean change from baseline

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

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

Figure 1. Study III ACR 20 Responses over 52 Weeks



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

In Study V with MTX naïve patients with recent onset rheumatoid arthritis, the combination treatment with HUMIRA plus MTX led to greater percentages of patients achieving ACR responses than either MTX monotherapy or HUMIRA monotherapy at Week 52 and responses were sustained at Week 104 (see Table 3).

Table 3: ACR Response in Study V (Percent of Patients)

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

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

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

Radiographic Response

In Study III, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and Joint Space Narrowing (JSN) score, at month 12 compared to baseline. At baseline, the median TSS was approximately 55 in the placebo and 40 mg every other week groups. The results are shown in Table 4. HUMIRA/MTX treated patients demonstrated less radiographic progression than patients receiving MTX alone at 52 weeks.

Table 4. Radiographic Mean Changes Over 12 Months in Study III

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

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

** Based on rank analysis

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

In Study V, structural joint damage was assessed as in Study III. Greater inhibition of radiographic progression, as assessed by changes in TSS, erosion score and JSN was observed in the HUMIRA/MTX combination group as compared to either the MTX or HUMIRA monotherapy group at Week 52 as well as at Week 104 (see Table 5).

Table 5: Radiographic Mean Change* in Study V

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

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

Physical Function Response

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

In Study III, the mean (95% CI) improvement in HAQ-DI from baseline at Week 52 was 0.60 (0.55, 0.65) for the HUMIRA patients and 0.25 (0.17, 0.33) for placebo/MTX ($p < 0.001$) patients. Eighty-two percent of HUMIRA-treated patients who achieved a 0.5 or greater improvement in HAQ-DI at Week 52 in the double-blind portion of the study maintained that improvement through Week 104 of open-label treatment. Improvement in SF-36 was also maintained through Week 104.

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

Psoriatic Arthritis

The safety and efficacy of HUMIRA was assessed in two randomized, double-blind, placebo controlled studies in 413 patients with psoriatic arthritis. Study PsA-I enrolled 313 adult patients with moderately to severely active psoriatic arthritis (>3 swollen and >3 tender joints) who had an inadequate response to NSAID therapy in one of the following forms: (1) distal interphalangeal (DIP) involvement (N=23); (2) polyarticular arthritis (absence of rheumatoid nodules and presence of psoriasis) (N=210); (3) arthritis mutilans (N=1); (4) asymmetric psoriatic arthritis (N=77); or (5) ankylosing spondylitis-like (N=2). Patients on MTX therapy (158 of 313 patients) at enrollment (stable dose of ≤30 mg/week for >1 month) could continue MTX at the same dose. Doses of HUMIRA 40 mg or placebo every other week were administered during the 24-week double-blind period of the study.

Compared to placebo, treatment with HUMIRA resulted in improvements in the measures of disease activity (see Tables 6 and 7). Among patients with psoriatic arthritis who received HUMIRA, the clinical responses were apparent in some patients at the time of the first visit (two weeks). Similar responses were seen in patients with each of the subtypes of psoriatic arthritis, although few patients were enrolled with the arthritis mutilans and

ankylosing spondylitis-like subtypes. Responses were similar in patients who were or were not receiving concomitant MTX therapy at baseline.

Patients with psoriatic involvement of at least three percent body surface area (BSA) were evaluated for Psoriatic Area and Severity Index (PASI) responses. At 24 weeks, the proportions of patients achieving a 75% or 90% improvement in the PASI were 59% and 42% respectively, in the HUMIRA group (N=69), compared to 1% and 0% respectively, in the placebo group (N=69) (p<0.001). PASI responses were apparent in some patients at the time of the first visit (two weeks). Responses were similar in patients who were or were not receiving concomitant MTX therapy at baseline.

Table 6: ACR Response in PsA-I (Percent of Patients)

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

* p<0.001 for all comparisons between HUMIRA and placebo

Table 7: Components of Disease Activity in PsA-I

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

* p<0.001 for HUMIRA vs. placebo comparisons based on median changes
a Scale 0-78
b Scale 0-76
c Visual analog scale; 0=best, 100=worst
d Disability Index of the Health Assessment Questionnaire; 0=best, 3=worst; measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity.
e Normal range: 0-0.287 mg/dL

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

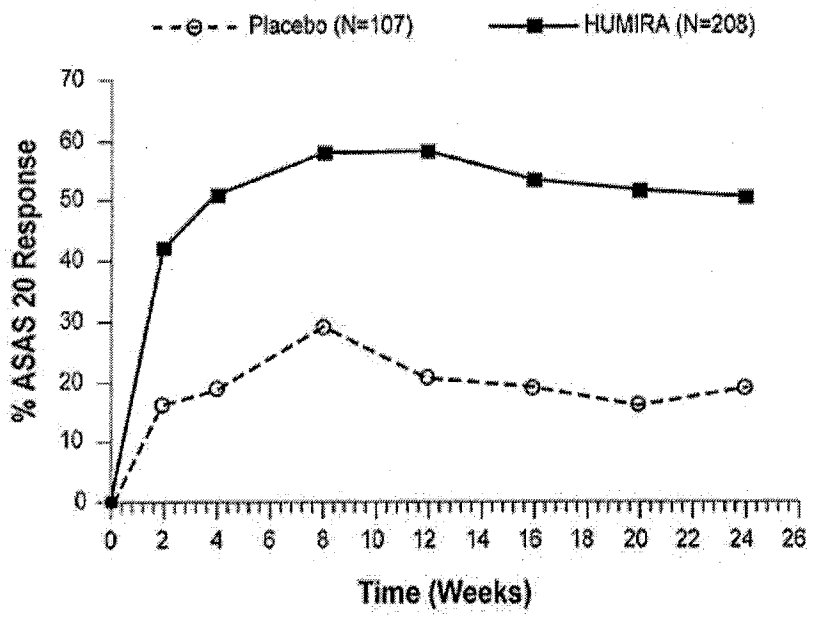
Ankylosing Spondylitis

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

Improvement in measures of disease activity was first observed at Week 2 and maintained through 24 weeks as shown in Figure 2 and Table 8.

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

Figure 2. ASAS 20 Response By Visit, Study VI



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

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

Table 8. Components of Ankylosing Spondylitis Disease Activity

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

a Percent of subjects with at least a 20% and 10-unit improvement measured on a Visual Analog Scale (VAS) with 0 = "none" and 100 = "severe"

b mean of questions 5 and 6 of BASDAI (defined in 'd')

c Bath Ankylosing Spondylitis Functional Index

d Bath Ankylosing Spondylitis Disease Activity Index

e Bath Ankylosing Spondylitis Metrology Index

f C-Reactive Protein (mg/dL)

* statistically significant for comparisons between HUMIRA and placebo at Week 24

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

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

INDICATIONS AND USAGE

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

HUMIRA is indicated for reducing signs and symptoms of active arthritis in patients with psoriatic arthritis. HUMIRA can be used alone or in combination with DMARDs.

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

CONTRAINDICATIONS

HUMIRA should not be administered to patients with known hypersensitivity to HUMIRA or any of its components.

WARNINGS

Serious Infections

SERIOUS INFECTIONS, SEPSIS, TUBERCULOSIS AND RARE CASES OF OPPORTUNISTIC INFECTIONS, INCLUDING FATALITIES, HAVE BEEN REPORTED WITH THE USE OF TNF BLOCKING AGENTS INCLUDING HUMIRA. MANY OF THE SERIOUS INFECTIONS HAVE OCCURRED IN PATIENTS ON CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO THEIR RHEUMATOID ARTHRITIS, COULD PREDISPOSE THEM TO INFECTIONS.

TREATMENT WITH HUMIRA SHOULD NOT BE INITIATED IN PATIENTS WITH ACTIVE INFECTIONS INCLUDING CHRONIC OR LOCALIZED INFECTIONS. PATIENTS WHO DEVELOP A NEW INFECTION WHILE UNDERGOING TREATMENT WITH HUMIRA SHOULD BE MONITORED CLOSELY. ADMINISTRATION OF HUMIRA SHOULD BE DISCONTINUED IF A PATIENT DEVELOPS A SERIOUS INFECTION. PHYSICIANS SHOULD EXERCISE CAUTION WHEN CONSIDERING THE USE OF HUMIRA IN PATIENTS WITH A HISTORY OF RECURRENT INFECTION OR UNDERLYING CONDITIONS WHICH MAY PREDISPOSE THEM TO INFECTIONS, OR PATIENTS WHO HAVE RESIDED IN REGIONS WHERE TUBERCULOSIS AND HISTOPLASMOSIS ARE ENDEMIC (see PRECAUTIONS- Tuberculosis and ADVERSE REACTIONS - Infections). THE BENEFITS AND RISKS OF HUMIRA TREATMENT SHOULD BE CAREFULLY CONSIDERED BEFORE INITIATION OF HUMIRA THERAPY.

Use with Anakinra

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

Hepatitis B Virus Reactivation

Use of TNF blockers, including HUMIRA, has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF blocker therapy. Prescribers should exercise

caution in prescribing TNF blockers for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with TNF blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, HUMIRA should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. Therefore, prescribers should exercise caution when considering resumption of HUMIRA therapy in this situation and monitor patients closely.

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. Prescribers should exercise caution in considering the use of HUMIRA in patients with preexisting or recent-onset central nervous system demyelinating disorders.

Malignancies

In the controlled portions of clinical trials of some TNF-blocking agents, including HUMIRA, more cases of malignancies have been observed among patients receiving those TNF blockers compared to control patients. During the controlled portions of HUMIRA trials in patients with moderately to severely active RA, malignancies, other than lymphoma and non-melanoma skin cancer, were observed at a rate (95% confidence interval) of 0.7 (0.4, 1.3)/100 patient-years among 1922 HUMIRA-treated patients versus a rate of 0.4 (0.1, 1.2)/100 patient-years among 947 control patients (median duration of treatment of 5.6 months for HUMIRA-treated patients and 5.2 months for control-treated patients). The size of the control group and limited duration of the controlled portions of studies precludes the ability to draw firm conclusions. In the controlled and uncontrolled open-label portions of the clinical trials of HUMIRA, the more frequently observed malignancies, other than lymphoma and non-melanoma skin cancer, were breast, colon, prostate, lung and uterine. These malignancies in HUMIRA-treated and control-treated patients were similar in type and number to what would be expected in the general population.[6] During the controlled portions of HUMIRA rheumatoid arthritis trials, the rate (95% confidence interval) of non-melanoma skin cancers was 0.9 (0.56, 1.55)/100 patient-years among HUMIRA-treated patients and 0.3 (0.07, 1.07)/100 patient-years among control patients. The potential role of TNF blocking therapy in the development of malignancies is not known.[4,5]

In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving TNF blockers compared to control patients. In controlled trials in patients with rheumatoid arthritis, 2 lymphomas were observed among 1922

HUMIRA-treated patients versus 1 among 947 control patients. In combining the controlled and uncontrolled open-label portions of these clinical trials with a median duration of approximately 3 years, including 3042 patients and over 8500 patient-years of therapy, the observed rate of lymphomas is approximately 0.15/100 patient-years. This is approximately 4-fold higher than expected in the general population.[6] Rates in clinical trials for HUMIRA cannot be compared to rates of clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. Patients with rheumatoid arthritis, particularly those with highly active disease, are at a higher risk for the development of lymphoma.

Hypersensitivity Reactions

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

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 (see **ADVERSE REACTIONS, Other Adverse Reactions**). The causal relationship of these reports to HUMIRA remains unclear. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g. persistent fever, bruising, bleeding, pallor) while on HUMIRA. Discontinuation of HUMIRA therapy should be considered in patients with confirmed significant hematologic abnormalities.

PRECAUTIONS

Information to Patients

The first injection should be performed under the supervision of a qualified health care professional. If a patient or caregiver is to administer HUMIRA, he/she should be instructed in injection techniques and their ability to inject subcutaneously should be assessed to ensure the proper administration of HUMIRA (see **HUMIRA, PATIENT INFORMATION LEAFLET**). A puncture-resistant container for disposal of needles and syringes should be used. Patients or caregivers should be instructed in the technique as well as proper syringe and needle disposal, and be cautioned against reuse of these items.

Tuberculosis

As observed with other TNF blocking agents, tuberculosis associated with the administration of HUMIRA in clinical trials has been reported (see

WARNINGS). While cases were observed at all doses, the incidence of tuberculosis reactivations was particularly increased at doses of HUMIRA that were higher than the recommended dose.

Before initiation of therapy with HUMIRA, patients should be evaluated for active or latent tuberculosis infection with a tuberculin skin test. If latent infection is diagnosed, appropriate prophylaxis in accordance with the Centers for Disease Control and Prevention guidelines[7] should be instituted. 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.

Patients with 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.

Immunosuppression

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

Immunizations

No data are available on the effects of vaccination in patients receiving HUMIRA. Live vaccines should not be given concurrently with HUMIRA. No data are available on the secondary transmission of infection by live vaccines in patients receiving HUMIRA.

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, Autoantibodies**).

Drug Interactions

Methotrexate

HUMIRA has been studied in rheumatoid arthritis patients taking concomitant MTX (see **CLINICAL PHARMACOLOGY, Drug Interactions**). The data do not suggest the need for dose adjustment of either HUMIRA or MTX.

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, Serious Infections**).

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

Pregnancy

Pregnancy Category B

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

Pregnancy Registry

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

ADVERSE REACTIONS

General

The most serious adverse reactions were (see **WARNINGS**):

- Serious Infections
- Neurologic Events
- Malignancies

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

The proportion of patients who discontinued treatment due to adverse events during the double-blind, placebo-controlled portion of Studies I, II, III and IV was 7% for patients taking HUMIRA and 4% 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%).

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

Infections

In placebo-controlled rheumatoid arthritis trials, the rate of infection was 1 per patient-year in the HUMIRA-treated patients and 0.9 per patient-year in the placebo-treated patients. The infections consisted primarily of upper respiratory tract infections, bronchitis and urinary tract infections. Most patients continued on HUMIRA after the infection resolved. The incidence of serious infections was 0.04 per patient-year in HUMIRA treated patients and 0.02 per patient-year in placebo-treated patients. Serious infections

observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis (see **WARNINGS**).

In completed and ongoing global clinical studies that include over 13000 patients, the overall rate of tuberculosis is approximately 0.26 per 100 patient-years. In over 4500 patients in the US and Canada, the rate is approximately 0.07 per 100 patient-years. These studies include reports of miliary, lymphatic, peritoneal, as well as pulmonary tuberculosis. Most of the cases of tuberculosis occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease. Cases of opportunistic infections have also been reported in these clinical trials at an overall rate of approximately 0.075/100 patient-years. Some cases of opportunistic infections and tuberculosis have been fatal (see **WARNINGS**). In postmarketing experience, infections have been observed with various pathogens including viral, bacterial, fungal, and protozoal organisms. Infections have been noted in all organ systems and have been reported in patients receiving HUMIRA alone or in combination with immunosuppressive agents.

Malignancies

More cases of malignancy have been observed in HUMIRA-treated patients compared to control-treated patients in clinical trials (see **WARNINGS**).

Autoantibodies

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

Immunogenicity

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

In patients with AS, the rate of development of antibodies to adalimumab in adalimumab-treated patients was comparable to patients with RA.

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

Other Adverse Reactions

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

Table 9 summarizes events reported at a rate of at least 5% in patients treated with HUMIRA 40 mg every other week compared to placebo and with an incidence higher than placebo. Adverse event rates in patients treated with HUMIRA 40 mg weekly were similar to rates in patients treated with HUMIRA 40 mg every other week. In Study III, the types and frequencies of adverse events in the second year open-label extension were similar to those observed in the one-year double-blind portion.

Table 9. Adverse Events Reported by ≥ 5% of Patients Treated with HUMIRA During Placebo-controlled Period of Rheumatoid Arthritis Studies

Adverse Event (Preferred Term)	HUMIRA 40 mg subcutaneous Every Other Week (N = 705) Percentage	Placebo (N = 690) Percentage
Respiratory		
Upper respiratory infection	17	13
Sinusitis	11	9
Flu syndrome	7	6
Gastrointestinal		
Nausea	9	8
Abdominal pain	7	4
Laboratory Tests*		
Laboratory test abnormal	8	7
Hypercholesterolemia	6	4
Hyperlipidemia	7	5
Hematuria	5	4
Alkaline phosphatase increased	5	3

Other		
Injection site pain	12	12
Headache	12	8
Rash	12	6
Accidental injury	10	8
Injection site reaction**	8	1
Back pain	6	4
Urinary tract infection	8	5
Hypertension	5	3

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

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

Other Adverse Events

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

Body As A Whole

Fever, infection, pain in extremity, pelvic pain, sepsis, surgery, thorax pain, tuberculosis reactivated

Cardiovascular System

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

Collagen Disorder

Lupus erythematosus syndrome

Digestive System

Cholecystitis, cholelithiasis, esophagitis, gastroenteritis, gastrointestinal disorder, gastrointestinal hemorrhage, hepatic necrosis, vomiting

Endocrine System

Parathyroid disorder

Hemic And Lymphatic System

Agranulocytosis, granulocytopenia, leukopenia, lymphoma like reaction, pancytopenia, polycythemia (see **WARNINGS - Hematologic Events**).

Metabolic And Nutritional Disorders

Dehydration, healing abnormal, ketosis, paraproteinemia, peripheral edema

Musculo-Skeletal System

Arthritis, bone disorder, bone fracture (not spontaneous), bone necrosis, joint disorder, muscle cramps, myasthenia, pyogenic arthritis, synovitis, tendon disorder

Neoplasia

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

Nervous System

Confusion, multiple sclerosis, paresthesia, subdural hematoma, tremor

Respiratory System

Asthma, bronchospasm, dyspnea, lung disorder, lung function decreased, pleural effusion, pneumonia

Skin And Appendages

Cellulitis, erysipelas, herpes zoster

Special Senses

Cataract

Thrombosis

Thrombosis leg

Urogenital System

Cystitis, kidney calculus, menstrual disorder, pyelonephritis

HUMIRA has been studied in 395 patients with psoriatic arthritis in two placebo-controlled studies and in an open-label extension study. 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.

Ankylosing Spondylitis Clinical Trials

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 I-IV. In the clinical trials of patients with ankylosing spondylitis, elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving HUMIRA than in controls, both when HUMIRA was given as monotherapy and when it was used in combination with other immunosuppressive agents. Most elevations of ALT and AST observed were in the range of 1.5-3 times the upper limit of normal. In general, patients who developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or resolved with either

continuation or discontinuation of HUMIRA, or modification of concomitant medications.

Adverse Reaction Information from Spontaneous Reports

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

Hematologic Events

Thrombocytopenia (see **WARNINGS** , **Hematologic Events**).

Hypersensitivity Reactions

Anaphylaxis, angioneurotic edema (see **WARNINGS** , **Hypersensitivity Reactions**).

Respiratory disorders

Interstitial lung disease, including pulmonary fibrosis.

Skin Reactions

cutaneous vasculitis.

OVERDOSAGE

The maximum tolerated dose of HUMIRA 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.

DOSAGE AND ADMINISTRATION

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

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 injection technique.

The solution in the syringe or HUMIRA Pen should be carefully inspected visually for particulate matter and discoloration prior to subcutaneous

administration. If particulates and discolorations are noted, the product should not be used. HUMIRA does not contain preservatives; therefore, unused portions of drug remaining from the syringe should be discarded. NOTE: The needle cover of the syringe contains dry rubber (latex), which should not be handled by persons sensitive to this substance.

Patients using the prefilled syringe or HUMIRA Pen should be instructed to inject the full amount in the syringe (0.8 mL), which provides 40 mg of HUMIRA, according to the directions provided in the Patient Information Leaflet.

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

Instructions For Activating the Needle Stick Device

Cartons for institutional use contain a syringe and needle with a needle protection device (see **HOW SUPPLIED**). To activate the needle stick protection device after injection, hold the syringe in one hand and, with the other hand, slide the outer protective shield over the exposed needle until it locks into place.

Storage and Stability

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

HOW SUPPLIED

#	Name	Strength	Dosage Form	Appearance	Package Type	Package Qty	NDC
1	HUMIRA	40 MILLIGRAM	INJECTION, SOLUTION (C42945)		CARTON (C43182)	2 SYRINGE	0074-3799-02
2	HUMIRA	40 MILLIGRAM	INJECTION, SOLUTION (C42945)		CARTON (C43182)	1 SYRINGE	0074-3799-01

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

Patient Use Syringe Carton

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

HUMIRA Pen Carton

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

Institutional Use Syringe Carton

Each carton contains two alcohol preps and one dose tray. Each dose tray consists of a single-use, 1 mL prefilled glass syringe with a fixed 27 gauge ½ inch needle (with a needle stick protection device) providing 40 mg (0.8 mL) of HUMIRA. **The NDC number is 0074-3799-01**.

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HUMIRA®

(adalimumab)

Patient Information

Read this leaflet carefully before you start taking HUMIRA (**hu-mare-ah**). You should also read this leaflet each time you get your prescription refilled, in case something has changed. The information in this leaflet does not take the place of talking with your doctor before you start taking this medicine and at check ups. Talk to your doctor if you have any questions about your treatment with HUMIRA.

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

Serious infections, including tuberculosis, have occurred in patients receiving HUMIRA. Some patients have died as a result of these infections. Before starting HUMIRA your doctor should test you for tuberculosis. If your doctor prescribes any medicine for the treatment of confirmed or suspected tuberculosis infection, you should start taking it before beginning HUMIRA treatment and you need to take the full course prescribed.

Tell your doctor or seek medical treatment if you experience any signs or symptoms that may indicate you have developed an infection such as persistent cough, weight loss, fever, chills, congestion or flu-like symptoms.

Also see "**What important information do I need to know about side effects with HUMIRA?**" for information regarding other serious side effects.

What Is HUMIRA?

HUMIRA is a medicine that is used in people with moderate to severe rheumatoid arthritis (RA), with psoriatic arthritis (PsA), or with a type of arthritis called ankylosing spondylitis (ank-e-low-sing spond-e-lie-tis) (AS). RA is an inflammatory disease of the joints. PsA is an inflammatory disease of the joints and skin. AS is an inflammatory disease of the spine. People may be given other medicines for their disease before they are given HUMIRA.

How Does HUMIRA Work?

HUMIRA is a medicine called a *TNF blocker*, that is a type of protein that blocks the action of a substance your body makes called TNF-alpha. TNF-alpha (tumor necrosis factor alpha) is made by your body's immune system. People with RA, PsA, or AS have too much of it in their bodies. The extra TNF-alpha in your body can attack normal healthy body tissues and cause inflammation especially in the tissues in your bones, cartilage, and joints. HUMIRA helps reduce the signs and symptoms of RA (such as pain and swollen joints), may help prevent further damage to your bones and joints, and may help improve your ability to perform daily activities. In addition,

HUMIRA helps reduce the signs and symptoms of PsA (such as pain and swollen joints). HUMIRA helps reduce the signs and symptoms of AS (back pain and morning stiffness).

HUMIRA can block the damage that too much TNF-alpha can cause, and it 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.

Who Should Not Take HUMIRA?

You should not take HUMIRA if you have an allergy to HUMIRA or to any of its ingredients (including sodium phosphate, sodium citrate, citric acid, mannitol, and polysorbate 80). The needle cover on the prefilled syringe contains dry natural rubber. Tell your doctor if you have any allergies to rubber or latex.

What information should I share with my doctor before I start taking HUMIRA?

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, please ask your doctor.
  - If you are a carrier of or suspect that you may be infected with the hepatitis B virus.
- A history of infections that keep coming back or other conditions that might increase your risk of infections.
- If you have ever had tuberculosis (TB), 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 TB and perform a skin test.
- 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.

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

What Important Information Do I Need to Know About Side Effects with HUMIRA?

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 Infections

There have been rare cases where patients taking HUMIRA or other TNF-blocking agents have developed serious infections, including tuberculosis (TB) and infections caused by bacteria or fungi. Some patients have died when the bacteria that cause infections have spread throughout their body (sepsis). See "**What is the most important information I should know about HUMIRA?**" for additional information regarding infections.

Hepatitis B

Treatment with TNF-blocking agents such as HUMIRA may result in a reactivation of the hepatitis B virus in people who carry this virus in a dormant state. In some cases patients have died as a result of hepatitis B virus being reactivated. If you know or suspect you may be a carrier of hepatitis B virus, be sure to tell your doctor about this as this may impact the decision to start treatment with HUMIRA.

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.

Malignancies

There have been very rare cases of certain kinds of cancer in patients taking HUMIRA or other TNF blockers. People with more serious RA 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.

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.

Blood Problems

In some patients the body may fail to produce enough of the blood cells that help your body fight infections or help you to stop bleeding. If you develop a fever that doesn't go away, bruise or bleed very easily or look very pale, call your doctor right away. Your doctor may decide to stop treatment.

Heart Problems

You should tell your doctor if you have ever been treated for heart failure. If you have, your doctor may choose not to start you on HUMIRA, or may want to monitor you more closely. If you develop new or worsening problems like shortness of breath or swelling of your ankles or feet, you should call your doctor right away.

Allergic Reactions

In rare cases, patients taking HUMIRA have had severe allergic reactions leading to difficulty breathing and low blood pressure, or shock. Allergic reactions can happen after your first dose or may not happen until after you have taken HUMIRA many times. If you develop a severe rash, swollen face or difficulty breathing while taking HUMIRA, call your doctor right away or seek emergency care immediately.

What Are the Other More Common Side Effects with HUMIRA?

Many patients experience a reaction where the injection was given. These reactions are usually mild and include redness, rash, swelling, itching or bruising. Usually, the rash will go away within a few days. If the skin around the area where you injected HUMIRA still hurts or is swollen, try using a towel soaked with cold water on the injection site. If you have pain, redness or swelling around the injection site that doesn't go away within a few days or gets worse, call your doctor right away. Other side effects are upper respiratory infections (sinus infections), headache and nausea.

Can I Take HUMIRA If I Am Pregnant or Breast-feeding?

HUMIRA has not been studied in pregnant women or nursing mothers, so we don't know what the effects are on pregnant women or nursing babies. You should tell your healthcare provider if you are pregnant, become pregnant or are thinking about becoming pregnant. If you take this medication while you are pregnant, or if you become pregnant while taking HUMIRA you are encouraged to participate in a pregnancy registry to gather additional information about the use of HUMIRA during pregnancy by calling 1-877-311-8972.

Can I Take HUMIRA If I Am Taking Other Medicines for My RA, PsA, AS, or Other Conditions?

Yes, 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 should also tell your doctor about any over-the-counter drugs, herbal medicines and vitamin and mineral supplements you are taking.

You should not take HUMIRA with other TNF blockers. If you have questions, ask your doctor.

How Do I Take HUMIRA?

You take HUMIRA by giving yourself an injection under the skin once every other week, or more frequently (every week) if your doctor tells you to. If you accidentally take more HUMIRA than you were told to take, you should call your doctor. Make sure you have been shown how to inject HUMIRA before you do it yourself. You can call your doctor or the HUMIRA Patient Resource Center at 1-800-4HUMIRA (448-6472) if you have any questions

about giving yourself an injection. Someone you know can also help you with your injection. Remember to take this medicine just as your doctor has told you and do not miss any doses.

What Should I Do If I Miss a Dose of HUMIRA?

If you forget to take HUMIRA when you are supposed to, inject the next dose right away. Then, take your next dose when your next scheduled dose is due. This will put you back on schedule.

Is One Time Better Than Another for Taking HUMIRA?

Always follow your doctor's instructions about when and how often to take HUMIRA. To help you remember when to take HUMIRA, you can mark your calendar ahead of time with the stickers provided in the back of the patient information booklet. For other information and ideas you can enroll in a patient support program by calling the HUMIRA Patient Resource Center at 1-800-4HUMIRA (448-6472).

What Do I Need to Do to Prepare and Give an Injection of HUMIRA?

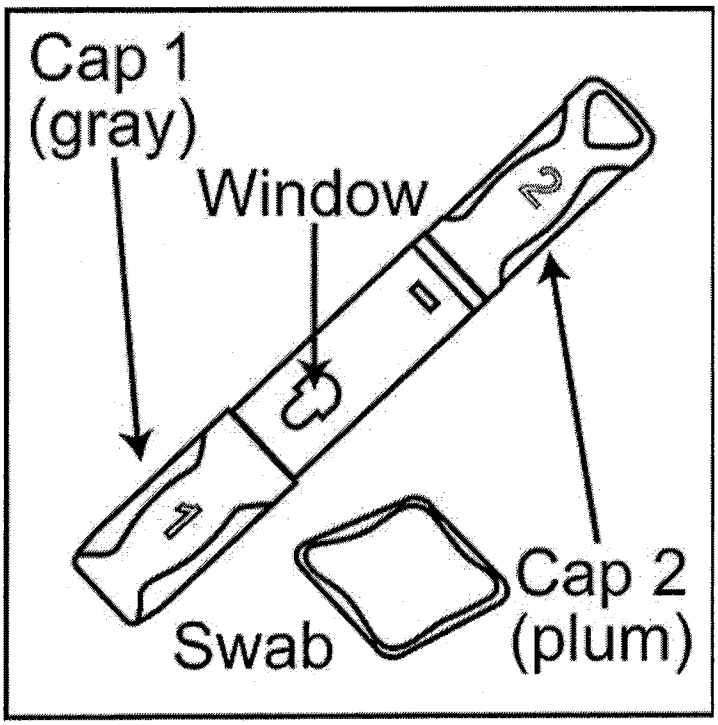
IF YOU ARE USING THE HUMIRA PEN

1) Setting up for an injection

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

You will need the following items for each dose:

- 1 HUMIRA Pen
- 1 alcohol prep (swab)



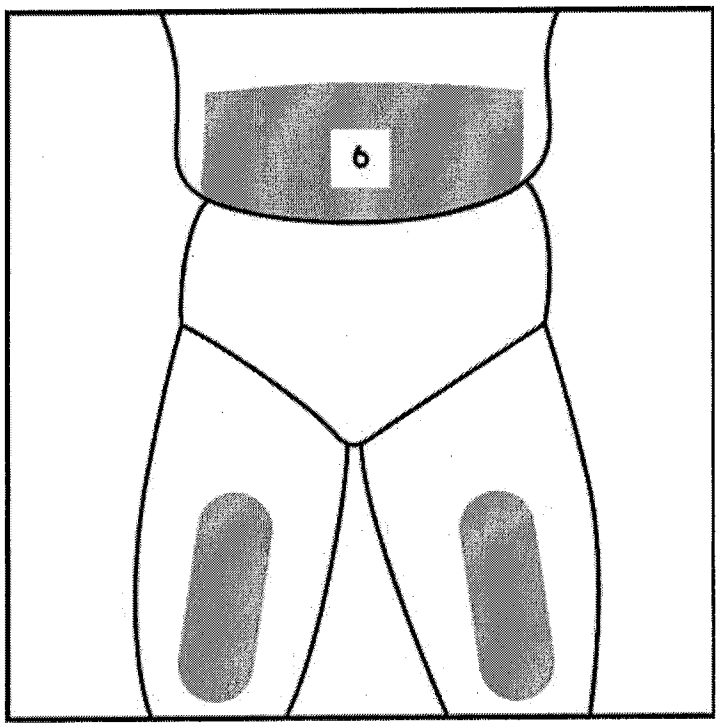
If you do not have all of the pieces you need to give yourself an injection, call your pharmacist. Use only the items provided in the box your HUMIRA comes in.

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

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

2) Choosing and preparing an injection site

- Wash your hands 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.

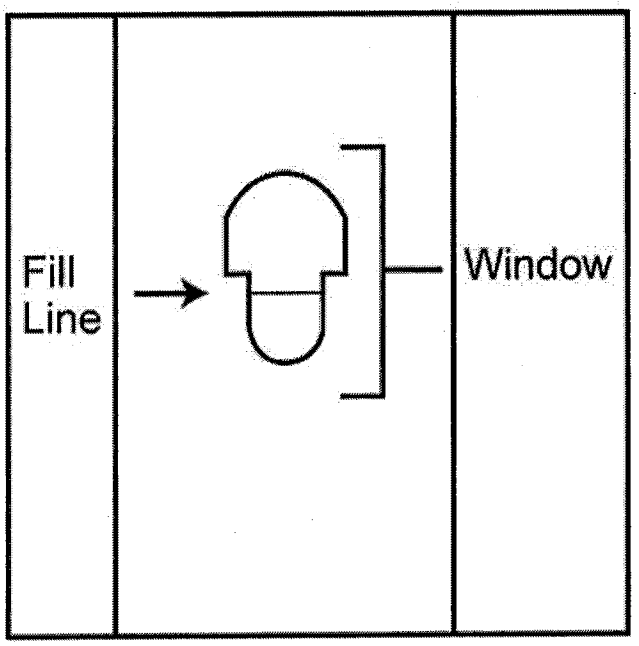


- Wipe the site where HUMIRA is to be injected with an alcohol prep (swab), using a circular motion. Do NOT touch this area again until you are ready to inject.

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

- Hold the Pen with the gray cap pointing up. Examine the solution through the windows on the side of the Pen to make sure the liquid is clear and colorless. Do not use a Pen if the liquid is cloudy or discolored or has flakes or particles in it. Do not use if frozen.
- Hold the Pen with the gray cap pointed down. Check to make sure that the amount of liquid in the Pen is the same or close to the fill line visible through the window. The fill line represents a full dose of the product. The top of the liquid may be curved. If the Pen does not have the correct amount of liquid, DO NOT USE THAT PEN. Call your pharmacist.

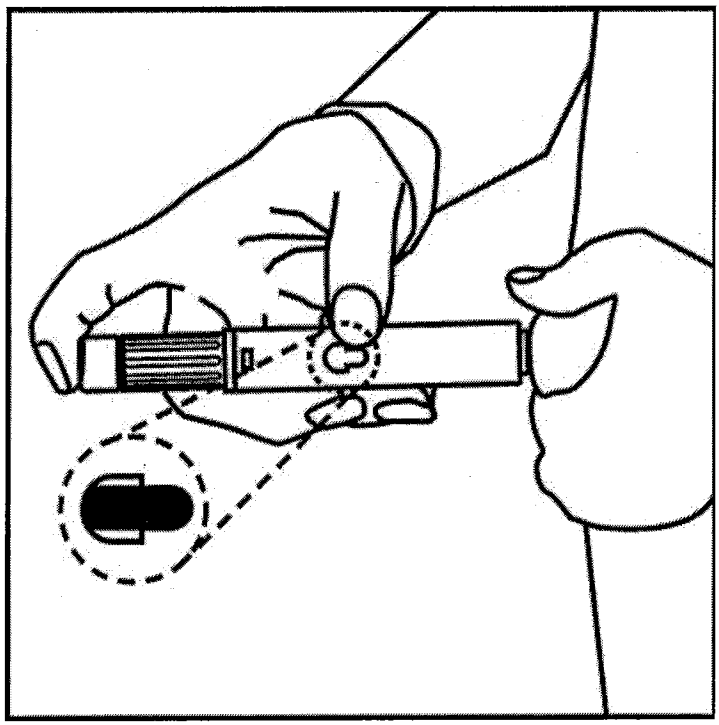
4) Injecting HUMIRA

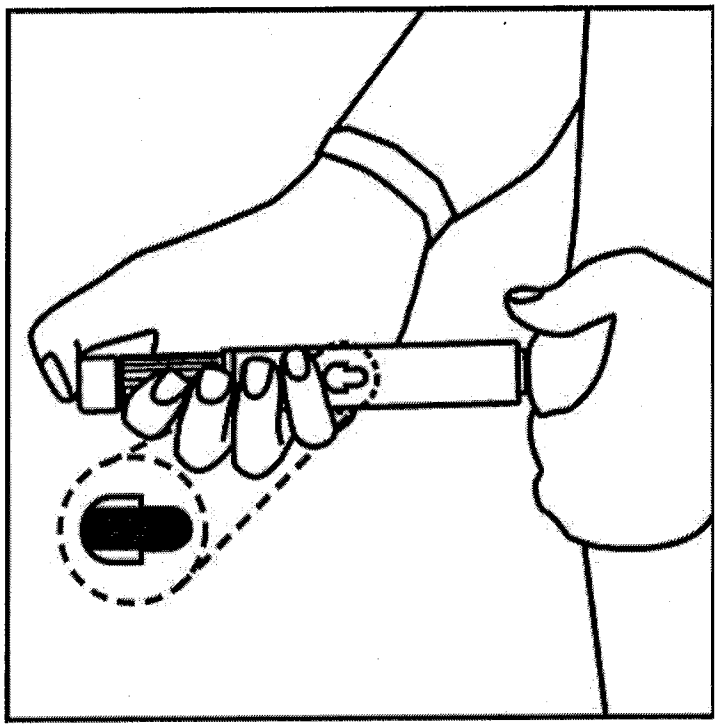


Hold the Pen with one hand. With your other hand, remove the gray cap (1) and discard cap. Pull the cap straight off. Do not twist the cap. Check that the small gray needle cover of the syringe has come off with the cap. After removal, the needle cover is held in the cap. Do not try to touch the needle housed in the barrel. The white needle sleeve will now be exposed. 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.

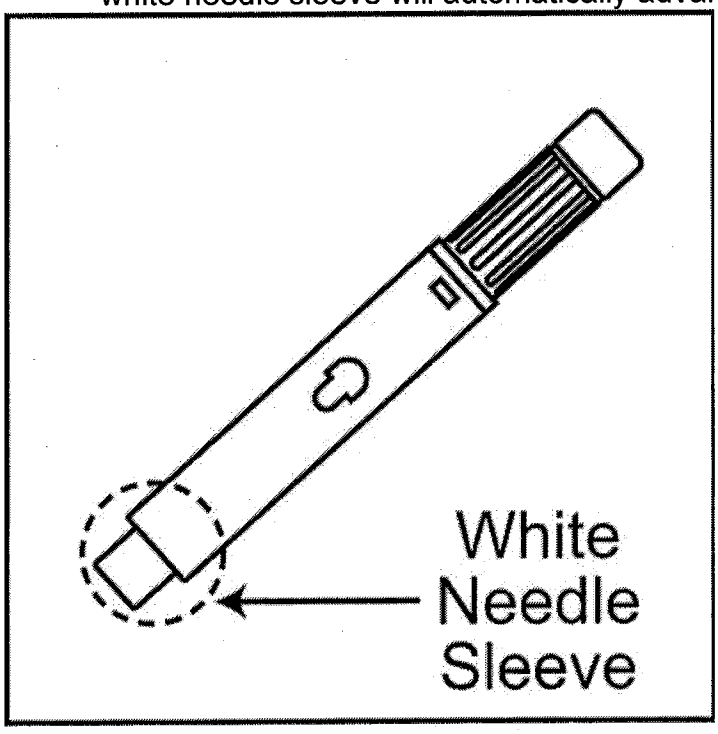
- Remove the plum safety cap (2) to expose the plum colored activation button at the top. Pull the cap straight off. Do not twist the cap. The Pen is now ready to use. Please note that the Pen is activated after removing cap 2 and that pressing the button under cap 2 will immediately result in discharge of medication. Do not press the button until properly positioned. **DO NOT RECAP as this could cause the unit to discharge.**
- Position the Pen so that the window is in view.

- With your free hand, gently squeeze a sizable area of the cleaned skin at the injection site, creating a platform on which to position the Pen.
- Position the white end of the Pen at a 90° angle flush against the platform of skin. Position the Pen so that it will not inject the needle into your fingers.
- With your index finger, press the plum colored button to begin the injection. You may also use your thumb to press the plum colored button to begin the injection. Try not to cover the window. Note that you will hear a 'click' when you press the button, which indicates the start of the injection. Keep pressing and continue to hold the Pen with steady pressure on the injection site until the process is finished. This can take up to 10 seconds. It is important to maintain steady pressure at the injection site for the entire period of time.





- You will know that the injection has finished when the yellow indicator in the side window appears in full view and stops.
- When the injection is finished, pull the Pen from the skin. The white needle sleeve will automatically advance over the needle tip.



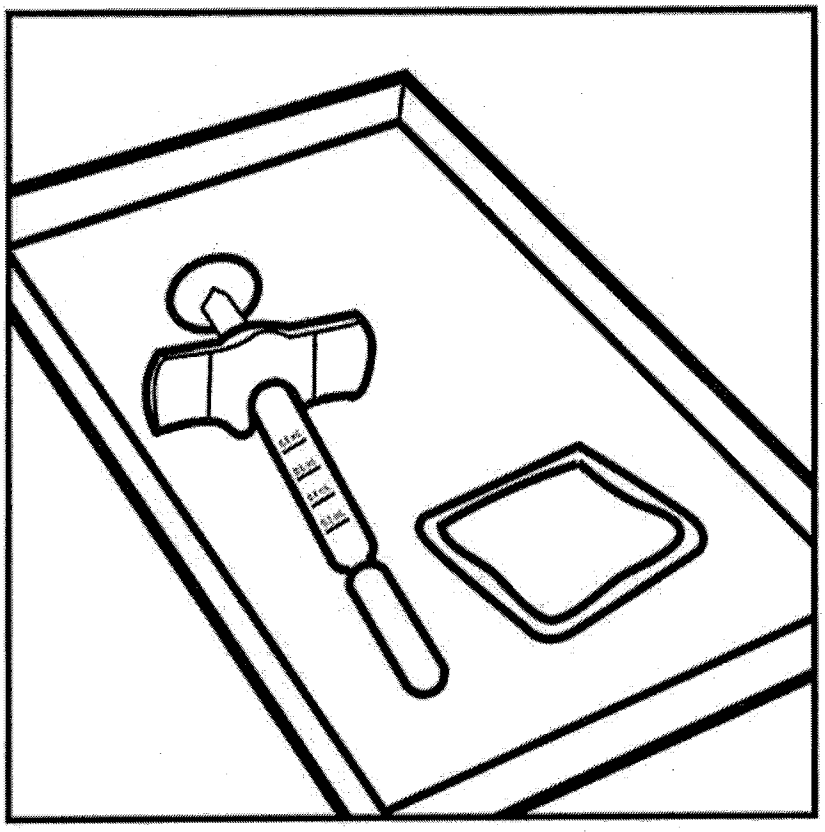
- Press a cotton ball over the injection site and hold it for 10 seconds. Do **NOT** rub the injection site. If you have slight bleeding, do not be alarmed.
- Dispose of the Pen immediately.

- Do not try to touch the needle. The white needle sleeve is there to prevent you from touching the needle. (See **How Do I Dispose of Syringes and Needles?**)

IF YOU ARE USING THE PREFILLED SYRINGE

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

You will need the following items for each dose:
- A dose tray containing a prefilled syringe of HUMIRA with a fixed needle
- 1 alcohol prep



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 comes in.
- Check and make sure the name HUMIRA appears on the dose tray and prefilled syringe label.

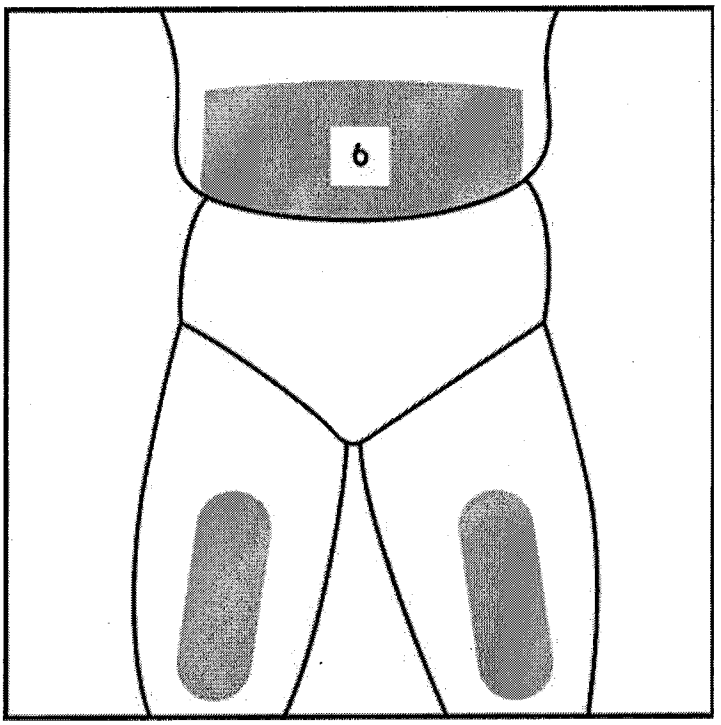
- Check the expiration date on the dose tray label and prefilled syringe to make sure the date has not passed. Do not use a prefilled syringe if the date has passed.
- Make sure the liquid in the prefilled syringe is clear and colorless. Do not use a prefilled syringe if the liquid is cloudy or discolored or has flakes or particles in it.
- Have a puncture proof container nearby for disposing of used needles and syringes.

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

2) Choosing and Preparing an Injection Site

- Wash your hands 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.



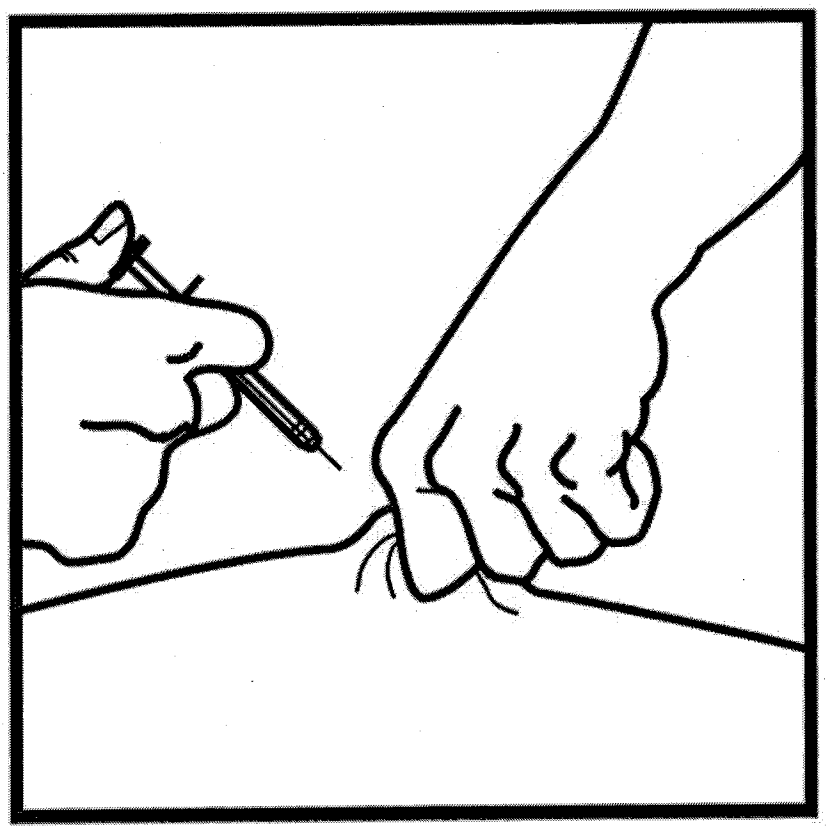
- Wipe the site where HUMIRA is to be injected with an alcohol prep, using a circular motion. Do NOT touch this area again until you are ready to inject.

3) How to Prepare Your HUMIRA Dose for Injection with a Prefilled Syringe

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

4) Injecting HUMIRA

- With your other hand, gently pinch the cleaned area of skin and hold it firmly. Hold the syringe like a pencil at about a 45° 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. Pull back slightly on the plunger, if blood appears in the syringe it means that you have entered a blood vessel. Do not inject HUMIRA. Withdraw the needle and repeat the steps to choose and clean a new injection site. DO NOT use the same syringe; discard it 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 keeping it at the same angle it was when it was inserted.

- Press a cotton ball over the injection site and hold it for 10 seconds. Do **NOT** rub the injection site. If you have slight bleeding, do not be alarmed.
- Dispose of the syringe immediately. (See **How Do I Dispose of Syringes and Needles?**)

How Do I Dispose of Syringes and Needles?

You should always check with your healthcare provider for instructions on how to properly dispose of used needles and syringes. You should follow any special state or local laws regarding the proper disposal of needles and syringes. **DO NOT throw the needle or syringe in the household trash or recycle**.

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

How Do I Store HUMIRA?

Store at 2°C-8°C/36-46°F (in a refrigerator) in the original container until it is used. Protect from light. **Do not freeze HUMIRA**. Refrigerated HUMIRA remains stable until the expiration date printed on the prefilled syringe or Pen. If you need to take it with you, such as when traveling, store it in a cool carrier with an ice pack and protect it from light.

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

Keep HUMIRA, injection supplies, and all other medicines out of the reach of children.

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