

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
125057Orig1s322

Trade Name: HUMIRA

Generic or adalimumab

Proper Name:

Sponsor: AbbVie Inc.

Approval Date: 04/24/2013

Indication:

HUMIRA is a tumor necrosis factor (TNF) blocker indicated for treatment of:
Rheumatoid Arthritis (RA) - Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.

Juvenile Idiopathic Arthritis (JIA) - reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 4 years of age and older.

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

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

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

Ulcerative Colitis (UC) - Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers.

Plaque Psoriasis (Ps) - The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systematic therapies are medically less appropriate.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057Orig1s322

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	X
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	X
Medical Review(s)	
Chemistry Review(s)	X
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125057Orig1s322

APPROVAL LETTER



BLA 125057/322

SUPPLEMENT APPROVAL

AbbVie Inc.
1 N. Waukegan Road
Bldg AP50; Dept. PA71
North Chicago, IL 60064-6220

Attention: Gresham Weatherly, Ph.D.
Associate Director, CMC Regulatory Affairs

Dear Dr. Weatherly:

Please refer to your Supplemental Biologics License Application (sBLA), dated November 16, 2012, received November 16, 2012, submitted under section 351(a) of the Public Health Service Act for Humira™ (adalimumab).

We also acknowledge receipt of your amendments dated March 18, 21, and 28, and April 22, 2013.

This Prior Approval supplemental biologics application provides for the addition of the 40 mg vial for institutional use only and to update the How Supplied section of the package insert with information regarding this new presentation.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert, text for Instructions for Use, text for the Medication Guide) and include the labeling changes proposed in any pending “Changes Being Effected” (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this BLA, including pending “Changes Being Effected” (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on March 18, 2013, as soon as they are available, but no more than 30 days after they are printed.

Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).” Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. Approval of this submission by FDA is not required before the labeling is used.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Sadaf Nabavian, Regulatory Project Manager, at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.,
Director
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BADRUL A CHOWDHURY
04/24/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125057Orig1s322

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

HUMIRA (adalimumab) injection, for subcutaneous use
Initial U.S. Approval: 2002

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

See full prescribing information for complete boxed warning.

SERIOUS INFECTIONS (5.1, 6.1):

- Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens.
- Discontinue HUMIRA if a patient develops a serious infection or sepsis during treatment.
- Perform test for latent TB; if positive, start treatment for TB prior to starting HUMIRA.
- Monitor all patients for active TB during treatment, even if initial latent TB test is negative.

MALIGNANCY (5.2):

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

RECENT MAJOR CHANGES

Indications and Usage, Ulcerative Colitis (1.6) ----- 9/2012
Dosage and Administration, Ulcerative Colitis (2.4) ----- 9/2012
Dosage and Administration, General Considerations for Administration (2.7)
----- 4/2013

INDICATIONS AND USAGE

HUMIRA is a tumor necrosis factor (TNF) blocker indicated for treatment of:
Rheumatoid Arthritis (RA) (1.1):

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

Juvenile Idiopathic Arthritis (JIA) (1.2):

- Reducing signs and symptoms of moderately to severely active polyarticular JIA in pediatric patients 4 years of age and older.

Psoriatic Arthritis (PsA) (1.3):

- Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.

Ankylosing Spondylitis (AS) (1.4):

- Reducing signs and symptoms in adult patients with active AS.

Crohn's Disease (CD) (1.5):

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

Ulcerative Colitis (UC) (1.6):

- Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers.

Plaque Psoriasis (Ps) (1.7):

- The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.

DOSAGE AND ADMINISTRATION

- Administered by subcutaneous injection (2)

Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis (2.1):

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

Juvenile Idiopathic Arthritis (2.2):

- 15 kg (33 lbs) to < 30 kg (66 lbs) 20 mg every other week
- ≥ 30 kg (66 lbs) 40 mg every other week

Crohn's Disease and Ulcerative Colitis (2.3, 2.4):

- Initial dose (Day 1): 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days)
- Second dose two weeks later (Day 15): 80 mg
- Two weeks later (Day 29): Begin a maintenance dose of 40 mg every other week.
- For patients with Ulcerative Colitis only: Only continue HUMIRA in patients who have shown evidence of clinical remission by eight weeks (Day 57) of therapy.

Plaque Psoriasis (2.5):

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

DOSAGE FORMS AND STRENGTHS

- Injection: 40 mg/0.8 mL in a single-use prefilled pen (HUMIRA Pen) (3)
- Injection: 40 mg/0.8 mL in a single-use prefilled glass syringe (3)
- Injection: 20 mg/0.4 mL in a single-use prefilled glass syringe (3)
- Injection: 40 mg/0.8 mL in a single-use glass vial for institutional use only (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- *Serious infections* Do not start HUMIRA during an active infection. If an infection develops, monitor carefully, and stop HUMIRA if infection becomes serious (5.1)
- *Invasive fungal infections* For patients who develop a systemic illness on HUMIRA, consider empiric antifungal therapy for those who reside or travel to regions where mycoses are endemic (5.1)
- *Malignancies* Incidence of malignancies was greater in HUMIRA-treated patients than in controls (5.2)
- *Anaphylaxis or serious allergic reactions* may occur (5.3)
- *Hepatitis B virus reactivation* Monitor HBV carriers during and several months after therapy. If reactivation occurs, stop HUMIRA and begin antiviral therapy (5.4)
- *Demyelinating disease* Exacerbation or new onset, may occur (5.5)
- *Cytopenias, pancytopenia* Advise patients to seek immediate medical attention if symptoms develop, and consider stopping HUMIRA (5.6)
- *Heart failure* Worsening or new onset, may occur (5.8)
- *Lupus-like syndrome* Stop HUMIRA if syndrome develops (5.9)

ADVERSE REACTIONS

Most common adverse reactions (incidence >10%): infections (e.g. upper respiratory, sinusitis), injection site reactions, headache and rash (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- *Abatacept* Increased risk of serious infection (5.1, 5.11, 7.2)
- *Anakinra* Increased risk of serious infection (5.1, 5.7, 7.2)
- *Live vaccines* Avoid use with HUMIRA (5.10, 7.3)

See 17 for PATIENT COUNSELING INFORMATION and the FDA-approved Medication Guide

FULL PRESCRIBING INFORMATION: CONTENTS *

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

1 INDICATIONS AND USAGE

- 1.1 Rheumatoid Arthritis
- 1.2 Juvenile Idiopathic Arthritis
- 1.3 Psoriatic Arthritis
- 1.4 Ankylosing Spondylitis
- 1.5 Crohn's Disease
- 1.6 Ulcerative Colitis
- 1.7 Plaque Psoriasis

2 DOSAGE AND ADMINISTRATION

- 2.1 Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis
- 2.2 Juvenile Idiopathic Arthritis
- 2.3 Crohn's Disease
- 2.4 Ulcerative Colitis
- 2.5 Plaque Psoriasis
- 2.6 Monitoring to Assess Safety
- 2.7 General Considerations for Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Serious Infections
- 5.2 Malignancies
- 5.3 Hypersensitivity Reactions
- 5.4 Hepatitis B Virus Reactivation
- 5.5 Neurologic Reactions
- 5.6 Hematological Reactions
- 5.7 Use with Anakinra
- 5.8 Heart Failure
- 5.9 Autoimmunity
- 5.10 Immunizations
- 5.11 Use with Abatacept

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience

- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Methotrexate
- 7.2 Biological Products
- 7.3 Live Vaccines
- 7.4 Cytochrome P450 Substrates

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Rheumatoid Arthritis
- 14.2 Juvenile Idiopathic Arthritis
- 14.3 Psoriatic Arthritis
- 14.4 Ankylosing Spondylitis
- 14.5 Crohn's Disease
- 14.6 Ulcerative Colitis
- 14.7 Plaque Psoriasis

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

- 17.1 Patient Counseling
- 17.2 Instruction on Injection Technique

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death [see *Warnings and Precautions (5.1)*]. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:

- Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HUMIRA use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.
- Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.
- Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients with chronic or recurrent infection.

Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy [see *Warnings and Precautions (5.1)* and *Adverse Reactions (6.1)*].

MALIGNANCY

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

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis

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

1.2 Juvenile Idiopathic Arthritis

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

1.3 Psoriatic Arthritis

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

1.4 Ankylosing Spondylitis

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

1.5 Crohn's Disease

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

1.6 Ulcerative Colitis

HUMIRA is indicated for inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers [see *Clinical Studies (14.6)*].

1.7 Plaque Psoriasis

HUMIRA is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. HUMIRA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician [see *Boxed Warning and Warnings and Precautions (5)*].

2 DOSAGE AND ADMINISTRATION

HUMIRA is administered by subcutaneous injection.

2.1 Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis

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

2.2 Juvenile Idiopathic Arthritis

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

Pediatric Patients (4 to 17 years)	Dose
15 kg (33 lbs) to <30 kg (66 lbs)	20 mg every other week (20 mg Prefilled Syringe)
≥30 kg (66 lbs)	40 mg every other week (HUMIRA Pen or 40 mg Prefilled Syringe)

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

2.3 Crohn's Disease

The recommended HUMIRA dose regimen for adult patients with Crohn's disease (CD) is 160 mg initially on Day 1 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose of 40 mg every other week. Aminosalicylates and/or corticosteroids may be continued during treatment with HUMIRA. Azathioprine, 6-mercaptopurine (6-MP) [see *Warnings and Precautions (5.2)*] or MTX may be continued during treatment with HUMIRA if necessary. The use of HUMIRA in CD beyond one year has not been evaluated in controlled clinical studies.

2.4 Ulcerative Colitis

The recommended HUMIRA dose regimen for adult patients with ulcerative colitis (UC) is 160 mg initially on Day 1 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later (Day 15). Two weeks later (Day 29) continue with a dose of 40 mg every other week.

Only continue HUMIRA in patients who have shown evidence of clinical remission by eight weeks (Day 57) of therapy.

Aminosalicylates and/or corticosteroids may be continued during treatment with HUMIRA. Azathioprine and 6-mercaptopurine (6-MP) [see *Warnings and Precautions (5.2)*] may be continued during treatment with HUMIRA if necessary.

2.5 Plaque Psoriasis

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

2.6 Monitoring to Assess Safety

Prior to initiating HUMIRA and periodically during therapy, evaluate patients for active tuberculosis and tested for latent infection [see *Warnings and Precautions (5.1)*].

2.7 General Considerations for Administration

HUMIRA is intended for use under the guidance and supervision of a physician. A patient may self-inject HUMIRA if a physician determines that it is appropriate, and with medical follow-up, as necessary, after proper training in subcutaneous injection technique. Carefully inspect the solution in the HUMIRA Pen or prefilled syringe for particulate matter and discoloration prior to subcutaneous administration. If particulates and discolorations are noted, do not use the product. HUMIRA does not contain preservatives; therefore,

discard unused portions of drug remaining from the syringe. NOTE: Instruct patients sensitive to latex not to handle the needle cover of the syringe because it contains dry rubber (latex).

Instruct patients using the HUMIRA Pen or prefilled syringe to inject the full amount in the syringe (0.8 mL), which provides 40 mg of HUMIRA, according to the directions provided in the Instructions for Use [see *Instructions for Use*].

Instruct patients (15 kg to <30 kg) using the pediatric pre-filled syringe, or their caregivers, to inject the full amount in the syringe (0.4 mL), which provides 20 mg of HUMIRA, according to the directions provided in the Instructions for Use.

Rotate injection sites and do not give injections into areas where the skin is tender, bruised, red or hard.

The HUMIRA institutional use vial is for use and administration within an institutional setting only, such as a hospital, physician's office or clinic. Withdraw the dose using a sterile needle and syringe and administer promptly by a healthcare provider within an institutional setting. Only administer one dose per vial. The vial does not contain preservatives; therefore, discard unused portions.

3 DOSAGE FORMS AND STRENGTHS

• Pen

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

• Prefilled Syringe

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

Injection: A single-use, 1 mL prefilled glass syringe with a fixed 27 gauge ½ inch needle, providing 20 mg (0.4 mL) of HUMIRA.

• Institutional Use Vial

Injection: A single-use, glass vial, providing 40 mg (0.8 mL) of HUMIRA for institutional use only.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Patients treated with HUMIRA are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death [see *Boxed Warning*]. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

The concomitant use of a TNF blocker and abatacept or anakinra was associated with a higher risk of serious infections in patients with rheumatoid arthritis (RA); therefore, the concomitant use of HUMIRA and these biologic products is not recommended in the treatment of patients with RA [see *Warnings and Precautions (5.7, 5.11) and Drug Interactions (7.2)*].

Treatment with HUMIRA should not be initiated in patients with an active infection, including localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants (such as corticosteroids or methotrexate), may be at greater risk of infection. Consider the risks and benefits of treatment prior to initiating therapy in patients:

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

Tuberculosis

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

Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy. Prior to initiating HUMIRA, assess if treatment for latent tuberculosis is needed; and consider an induration of ≥ 5 mm a positive tuberculin skin test result, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG).

Consider anti-tuberculosis therapy prior to initiation of HUMIRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Strongly consider tuberculosis in the differential diagnosis in patients who develop a new infection during HUMIRA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Monitoring

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

Discontinue HUMIRA if a patient develops a serious infection or sepsis. For a patient who develops a new infection during treatment with HUMIRA, closely monitor them, perform a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and initiate appropriate antimicrobial therapy.

Invasive Fungal Infections

If patients develop a serious systemic illness and they reside or travel in regions where mycoses are endemic, consider invasive fungal infection in the differential diagnosis. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider appropriate empiric antifungal therapy, taking into account both the risk for severe fungal infection and the risks of antifungal therapy, while a diagnostic workup is being performed. To aid in the management of such patients, consider consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections.

5.2 Malignancies

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

Malignancies in Adults

In the controlled portions of clinical trials of some TNF-blockers, including HUMIRA, more cases of malignancies have been observed among TNF-blocker-treated adult patients compared to control-treated adult patients. During the controlled portions of 34 global HUMIRA clinical trials in adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC) and plaque psoriasis (Ps), malignancies, other than non-melanoma (basal cell and squamous cell) skin cancer, were observed at a rate (95% confidence interval) of 0.6 (0.38, 0.91) per 100 patient-years among 7304 HUMIRA-treated patients versus a rate of 0.6 (0.30, 1.03) per 100 patient-years among 4232 control-treated patients (median duration of treatment of 4 months for HUMIRA-treated patients and 4 months for control-treated patients). In 47 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, and Ps, the most frequently observed malignancies, other than lymphoma and NMSC, were breast, colon, prostate, lung, and melanoma. The malignancies in HUMIRA-treated patients in the controlled and uncontrolled portions of the studies were similar in type and number to what would be expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).¹

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

Non-Melanoma Skin Cancer

During the controlled portions of 34 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, and Ps, the rate (95% confidence interval) of NMSC was 0.7 (0.49, 1.08) per 100 patient-years among HUMIRA-treated patients and 0.2 (0.08, 0.59) per 100 patient-years among control-treated patients. Examine all patients, and in particular patients with a medical history of prior prolonged immunosuppressant therapy or psoriasis patients with a history of PUVA treatment for the presence of NMSC prior to and during treatment with HUMIRA.

Lymphoma and Leukemia

In the controlled portions of clinical trials of all the TNF-blockers in adults, more cases of lymphoma have been observed among TNF-blocker-treated patients compared to control-treated patients. In the controlled portions of 34 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC and Ps, 3 lymphomas occurred among 7304 HUMIRA-treated patients versus 1 among 4232 control-treated patients. In 47 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC and Ps with a median duration of approximately 0.6 years, including 23,036 patients and over 34,000 patient-years of HUMIRA, the observed rate of lymphomas was approximately 0.11 per 100 patient-years. This is approximately 3-fold higher than expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).¹ Rates of lymphoma in clinical trials of HUMIRA cannot be compared to rates of lymphoma in clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. Patients with RA and other chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF blockers. Post-marketing cases of acute and chronic

leukemia have been reported in association with TNF-blocker use in RA and other indications. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Malignancies in Pediatric Patients and Young Adults

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

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

5.3 Hypersensitivity Reactions

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

5.4 Hepatitis B Virus Reactivation

Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy. 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. For patients who are carriers of HBV and require treatment with TNF blockers, closely monitor such patients 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, stop HUMIRA and initiate effective anti-viral therapy with appropriate supportive treatment. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. Therefore, exercise caution when considering resumption of HUMIRA therapy in this situation and monitor patients closely.

5.5 Neurologic Reactions

Use of TNF blocking agents, including HUMIRA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis (MS) and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Exercise caution in considering the use of HUMIRA in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders.

5.6 Hematological Reactions

Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., thrombocytopenia, leukopenia) have been infrequently reported with HUMIRA. The causal relationship of these reports to HUMIRA remains unclear. Advise all patients 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. Consider discontinuation of HUMIRA therapy in patients with confirmed significant hematologic abnormalities.

5.7 Use with Anakinra

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

5.8 Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. Cases of worsening CHF have also been observed with HUMIRA. HUMIRA has not been formally studied in patients with CHF; however, in clinical

trials of another TNF blocker, a higher rate of serious CHF-related adverse reactions was observed. Exercise caution when using HUMIRA in patients who have heart failure and monitor them carefully.

5.9 Autoimmunity

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

5.10 Immunizations

In a placebo-controlled clinical trial of patients with RA, no difference was detected in anti-pneumococcal antibody response between HUMIRA and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with HUMIRA. Similar proportions of patients developed protective levels of anti-influenza antibodies between HUMIRA and placebo treatment groups; however, titers in aggregate to influenza antigens were moderately lower in patients receiving HUMIRA. The clinical significance of this is unknown. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving HUMIRA. It is recommended that JIA patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating HUMIRA therapy. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines.

5.11 Use with Abatacept

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

6 ADVERSE REACTIONS

The most serious adverse reactions described elsewhere in the labeling include the following:

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

6.1 Clinical Trials Experience

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.

The most common adverse reaction with HUMIRA was injection site reactions. In placebo-controlled trials, 20% of patients treated with HUMIRA developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 14% of patients receiving placebo. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation. The proportion of patients who discontinued treatment due to adverse reactions during the double-blind, placebo-controlled portion of studies in patients with RA (i.e., Studies RA-I, RA-II, RA-III and RA-IV) was 7% for patients taking HUMIRA and 4% for placebo-treated patients. The most common adverse reactions leading to discontinuation of HUMIRA in these RA studies were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%).

Infections

In the controlled portions of the 34 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC and Ps, the rate of serious infections was 4.6 per 100 patient-years in 7304 HUMIRA-treated patients versus a rate of 3.1 per 100 patient-years in 4232 control-treated patients. Serious infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis [see *Warnings and Precautions (5.1)*].

Tuberculosis and Opportunistic Infections

In 47 global controlled and uncontrolled clinical trials in RA, PsA, AS, CD, UC and Ps that included 23,036 HUMIRA-treated patients, the rate of reported active tuberculosis was 0.22 per 100 patient-years and the rate of positive PPD conversion was 0.08 per 100 patient-years. In a subgroup of 9396 U.S. and Canadian HUMIRA-treated patients, the rate of reported active TB was 0.07 per 100 patient-years and the rate of positive PPD conversion was 0.08 per 100 patient-years. These trials included reports of miliary, lymphatic, peritoneal, and pulmonary TB. Most of the TB cases occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease. In these global clinical trials, cases of serious opportunistic infections have been reported at an overall rate of 0.08 per 100 patient-years. Some cases of serious opportunistic infections and TB have been fatal [see *Warnings and Precautions (5.1)*].

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.

Liver Enzyme Elevations

There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers. In controlled Phase 3 trials of HUMIRA (40 mg SC every other week) in patients with RA, PsA, and AS with control period duration ranging from 4 to 104 weeks, ALT elevations $\geq 3 \times$ ULN occurred in 3.5% of HUMIRA-treated patients and 1.5% of control-treated patients. Since many of these patients in these trials were also taking medications that cause liver enzyme elevations (e.g., NSAIDs, MTX), the relationship between HUMIRA and the liver enzyme elevations is not clear. In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg, or 80 mg and 40 mg on Days 1 and 15, respectively, followed by 40 mg every other week) in patients with CD with control period duration ranging from 4 to 52 weeks, ALT elevations $\geq 3 \times$ ULN occurred in 0.9% of HUMIRA-treated patients and 0.9% of control-treated patients. In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg on Days 1 and 15 respectively, followed by 40 mg every other week) in patients with UC with control period duration ranging from 1 to 52 weeks, ALT elevations $\geq 3 \times$ ULN occurred in 1.5% of HUMIRA-treated patients and 1.0% of control-treated patients. In controlled Phase 3 trials of HUMIRA (initial dose of 80 mg then 40 mg every other week) in patients with Ps with control period duration ranging from 12 to 24 weeks, ALT elevations $\geq 3 \times$ ULN occurred in 1.8% of HUMIRA-treated patients and 1.8% of control-treated patients.

Immunogenicity

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

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

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

In patients with PsA, the rate of antibody development in patients receiving HUMIRA monotherapy was comparable to patients with RA; however, in patients receiving concomitant MTX the rate was 7% compared to 1% in RA.

In patients with CD, the rate of antibody development was 3%.

In patients with moderately to severely active UC, the rate of antibody development in patients receiving HUMIRA was 5%.

However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 ug/ml. Among the patients whose serum adalimumab levels were < 2 ug/ml (approximately 25% of total patients studied), the immunogenicity rate was 20.7%.

In patients with Ps, 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 ug/ml. Among the patients whose serum adalimumab levels were < 2 ug/ml (approximately 40% of total patients studied), the immunogenicity rate was 20.7%. In Ps patients who were on HUMIRA monotherapy and subsequently withdrawn from the treatment, the rate of antibodies to adalimumab after retreatment was similar to the rate observed prior to withdrawal.

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

Other Adverse Reactions

Rheumatoid Arthritis Clinical Studies

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

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

Table 1. Adverse Reactions Reported by $\geq 5\%$ of Patients Treated with HUMIRA During Placebo-Controlled Period of Pooled RA Studies (Studies RA-I, RA-II, RA-III, and RA-IV)

	HUMIRA 40 mg subcutaneous Every Other Week	Placebo

	(N=705)	(N=690)
Adverse Reaction (Preferred Term)		
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		
Headache	12%	8%
Rash	12%	6%
Accidental injury	10%	8%
Injection site reaction **	8%	1%
Back pain	6%	4%
Urinary tract infection	8%	5%
Hypertension	5%	3%
* Laboratory test abnormalities were reported as adverse reactions in European trials		
** Does not include injection site erythema, itching, hemorrhage, pain or swelling		

Less Common Adverse Reactions in Rheumatoid Arthritis Clinical Studies

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

Body As A Whole: Pain in extremity, pelvic pain, surgery, thorax pain

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

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

Endocrine System: Parathyroid disorder

Hemic And Lymphatic System: Agranulocytosis, polycythemia

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

Nervous System: Confusion, paresthesia, subdural hematoma, tremor

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

Special Senses: Cataract

Thrombosis: Thrombosis leg

Urogenital System: Cystitis, kidney calculus, menstrual disorder

Juvenile Idiopathic Arthritis Clinical Studies

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

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

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

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

Isolated mild to moderate elevations of liver aminotransferases (ALT more common than AST) were observed in children with JIA exposed to HUMIRA alone; liver enzyme test elevations were more frequent among those treated with the combination of HUMIRA and MTX than those treated with HUMIRA alone. In general, these elevations did not lead to discontinuation of HUMIRA treatment. In the JIA trial, 10% of patients treated with HUMIRA who had negative baseline anti-dsDNA antibodies developed positive titers after 48 weeks of treatment. No patient developed clinical signs of autoimmunity during the clinical trial.

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

Psoriatic Arthritis and Ankylosing Spondylitis Clinical Studies

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

Crohn's Disease Clinical Studies

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

Ulcerative Colitis Clinical Studies

HUMIRA has been studied in 1010 patients with ulcerative colitis (UC) in two placebo-controlled studies and one open-label extension study. The safety profile for patients with UC treated with HUMIRA was similar to the safety profile seen in patients with RA.

Plaque Psoriasis Clinical Studies

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

6.2 Postmarketing Experience

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

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

Hepato-biliary disorders: Liver failure

Immune system disorders: Sarcoidosis

Nervous system disorders: Demyelinating disorders (e.g., optic neuritis, Guillain-Barré syndrome), cerebrovascular accident

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

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

Vascular disorders: Systemic vasculitis, deep vein thrombosis

7 DRUG INTERACTIONS

7.1 Methotrexate

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

7.2 Biological Products

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

7.3 Live Vaccines

Avoid the use of live vaccines with HUMIRA [see *Warnings and Precautions (5.10)*].

7.4 Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNF α , IL-6) during chronic inflammation. It is possible for a molecule that antagonizes cytokine activity, such as adalimumab, to influence the formation of CYP450 enzymes. Upon initiation or discontinuation of HUMIRA in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

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

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

Juvenile Idiopathic Arthritis

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

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

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

8.5 Geriatric Use

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

10 OVERDOSAGE

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

11 DESCRIPTION

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

HUMIRA is supplied as a sterile, preservative-free solution of adalimumab for subcutaneous administration. The drug product is supplied as either a single-use, prefilled pen (HUMIRA Pen) or as a single-use, 1 mL prefilled glass syringe. Enclosed within the pen is a single-use, 1 mL prefilled glass syringe. The solution of HUMIRA is clear and colorless, with a pH of about 5.2.

Each prefilled syringe delivers 0.8 mL (40 mg) of drug product. Each 0.8 mL of HUMIRA contains 40 mg adalimumab, 4.93 mg sodium chloride, 0.69 mg monobasic sodium phosphate dihydrate, 1.22 mg dibasic sodium phosphate dihydrate, 0.24 mg sodium citrate, 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.

Each pediatric prefilled syringe delivers 0.4 mL (20 mg) of drug product. Each 0.4 mL of HUMIRA contains 20 mg adalimumab, 2.47 mg sodium chloride, 0.34 mg monobasic sodium phosphate dihydrate, 0.61 mg dibasic sodium phosphate dihydrate, 0.12 mg sodium citrate, 0.52 mg citric acid monohydrate, 4.8 mg mannitol, 0.4 mg polysorbate 80, and Water for Injection, USP. Sodium hydroxide added as necessary to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Adalimumab binds specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also lyses surface TNF expressing cells *in vitro* in the presence of complement. Adalimumab does not bind or inactivate lymphotoxin (TNF-beta). TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of patients with RA, JIA, PsA, and AS and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. Increased levels of TNF are also found in psoriasis plaques. In Ps, treatment with HUMIRA may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamic activities and the mechanism(s) by which HUMIRA exerts its clinical effects is unknown. Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC₅₀ of 1-2 X 10⁻¹⁰M).

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

The maximum serum concentration (C_{max}) and the time to reach the maximum concentration (T_{max}) were 4.7 ± 1.6 µg/mL and 131 ± 56 hours respectively, following a single 40 mg subcutaneous administration of HUMIRA to healthy adult subjects. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64%. The pharmacokinetics of adalimumab were linear over the dose range of 0.5 to 10.0 mg/kg following a single intravenous dose. The single dose pharmacokinetics of adalimumab in RA patients were determined in several studies with intravenous doses ranging from 0.25 to 10 mg/kg. The distribution volume (V_{ss}) ranged from 4.7 to 6.0 L. The systemic clearance of adalimumab is approximately 12 mL/hr. The mean terminal half-life was approximately 2 weeks, ranging from 10 to 20 days across studies. Adalimumab concentrations in the synovial fluid from five rheumatoid arthritis patients ranged from 31 to 96% of those in serum. In RA patients receiving 40 mg HUMIRA every other week, adalimumab mean steady-state trough concentrations of approximately 5 µg/mL and 8 to 9 µg/mL, were observed without and with methotrexate (MTX), respectively. MTX reduced adalimumab apparent clearance after single and multiple dosing by 29% and 44% respectively, in patients with RA. Mean serum adalimumab trough levels at steady state increased approximately proportionally with dose following 20, 40, and 80 mg every other week and every week subcutaneous dosing. In long-term studies with dosing more than two years, there was no evidence of changes in clearance over time. Adalimumab mean steady-state trough concentrations were slightly higher in psoriatic arthritis patients treated with 40 mg HUMIRA every other week (6 to 10 µg/mL and 8.5 to 12 µg/mL, without and with MTX, respectively) compared to the concentrations in RA patients treated with the same dose.

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

In patients with CD, the loading dose of 160 mg HUMIRA on Week 0 followed by 80 mg HUMIRA on Week 2 achieves mean serum adalimumab trough levels of approximately 12 µg/mL at Week 2 and Week 4. Mean steady-state trough levels of approximately 7 µg/mL were observed at Week 24 and Week 56 in CD patients after receiving a maintenance dose of 40 mg HUMIRA every other week. In patients with UC, the loading dose of 160 mg HUMIRA on Week 0 followed by 80 mg HUMIRA on Week 2 achieves mean serum adalimumab trough levels of approximately 12 µg/mL at Week 2 and Week 4. Mean steady-state trough level of approximately 8 µg/mL was observed at Week 52 in UC patients after receiving a dose of 40 mg HUMIRA every other week, and approximately 15 µg/mL at Week 52 in UC patients who increased to a dose of 40 mg HUMIRA every week.

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

Population pharmacokinetic analyses in patients with RA revealed that there was a trend toward higher apparent clearance of adalimumab in the presence of anti-adalimumab antibodies, and lower clearance with increasing age in patients aged 40 to >75 years. Minor increases in apparent clearance were also predicted in RA patients receiving doses lower than the recommended dose and in RA patients with high rheumatoid factor or CRP concentrations. These increases are not likely to be clinically important.

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES

14.1 Rheumatoid Arthritis

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

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

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

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

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

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

Clinical Response

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

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

	Study RA-II Monotherapy	Study RA-III Methotrexate Combination
--	----------------------------	--

Response	Placebo N=110	(26 weeks)		(24 and 52 weeks)	
		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 RA-I were similar to Study RA-III; patients receiving HUMIRA 40 mg every other week in Study RA-I also achieved ACR 20, 50 and 70 response rates of 65%, 52% and 24%, respectively, compared to placebo responses of 13%, 7% and 3% respectively, at 6 months (p<0.01).

The results of the components of the ACR response criteria for Studies RA-II and RA-III are shown in Table 3. ACR response rates and improvement in all components of ACR response were maintained to week 104. Over the 2 years in Study RA-III, 20% of HUMIRA patients receiving 40 mg every other week (EOW) achieved a major clinical response, defined as maintenance of an ACR 70 response over a 6-month period. ACR responses were maintained in similar proportions of patients for up to 5 years with continuous HUMIRA treatment in the open-label portion of Study RA-III.

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

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

^a 40 mg HUMIRA administered every other week

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

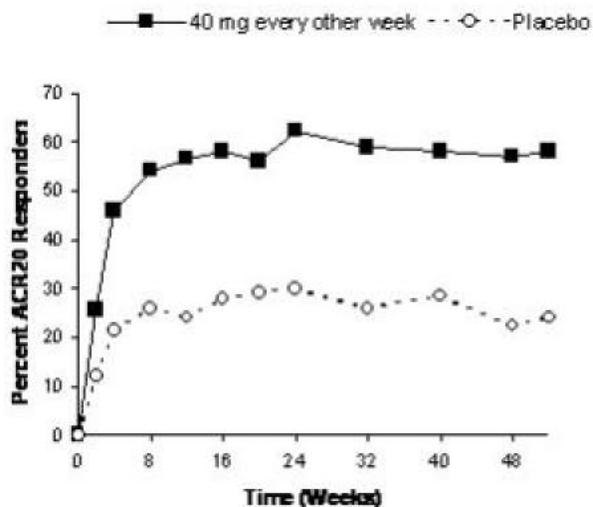
^c Disability Index of the Health Assessment Questionnaire; 0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity

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

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

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

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



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

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

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

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

^a Major clinical response is defined as achieving an ACR70 response for a continuous six month period

^b $p < 0.05$, HUMIRA/MTX vs. MTX for ACR 20

$p < 0.001$, HUMIRA/MTX vs. MTX for ACR 50 and 70, and Major Clinical Response

^c $p < 0.001$, HUMIRA/MTX vs. HUMIRA

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

Radiographic Response

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

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

	Placebo/MTX	HUMIRA/MTX 40 mg every other week	Placebo/MTX- HUMIRA/MTX (95% Confidence	P-value**

			Interval*)	
Total Sharp score	2.7	0.1	2.6 (1.4, 3.8)	<0.001
Erosion score	1.6	0.0	1.6 (0.9, 2.2)	<0.001
JSN score	1.0	0.1	0.9 (0.3, 1.4)	0.002

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

**Based on rank analysis

In the open-label extension of Study RA-III, 77% of the original patients treated with any dose of HUMIRA were evaluated radiographically at 2 years. Patients maintained inhibition of structural damage, as measured by the TSS. Fifty-four percent had no progression of structural damage as defined by a change in the TSS of zero or less. Fifty-five percent (55%) of patients originally treated with 40 mg HUMIRA every other week have been evaluated radiographically at 5 years. Patients had continued inhibition of structural damage with 50% showing no progression of structural damage defined by a change in the TSS of zero or less. In Study RA-V, structural joint damage was assessed as in Study RA-III. Greater inhibition of radiographic progression, as assessed by changes in TSS, erosion score and JSN was observed in the HUMIRA/MTX combination group as compared to either the MTX or HUMIRA monotherapy group at Week 52 as well as at Week 104 (see Table 6).

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

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

* mean (95% confidence interval)

^a p<0.001, HUMIRA/MTX vs. MTX at 52 and 104 weeks and for HUMIRA/MTX vs. HUMIRA at 104 weeks

^b p<0.01, for HUMIRA/MTX vs. HUMIRA at 52 weeks

Physical Function Response

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

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

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

14.2 Juvenile Idiopathic Arthritis

The safety and efficacy of HUMIRA were assessed in a multicenter, randomized, withdrawal, double-blind, parallel-group study in 171 children (4 to 17 years of age) with polyarticular juvenile idiopathic arthritis (JIA). In the study, the patients were stratified into two groups: MTX-treated or non-MTX-treated. All subjects had to show signs of active moderate or severe disease despite previous treatment with NSAIDs, analgesics, corticosteroids, or DMARDs. Subjects who received prior treatment with any biologic DMARDs were excluded from the study.

The study included four phases: an open-label lead in phase (OL-LI; 16 weeks), a double-blind randomized withdrawal phase (DB; 32 weeks), an open-label extension phase (OLE-BSA; up to 136 weeks), and an open-label fixed dose phase (OLE-FD; 16 weeks). In the first three phases of the study, HUMIRA was administered based on body surface area at a dose of 24 mg/m² up to a maximum total body dose of 40 mg subcutaneously (SC) every other week. In the OLE-FD phase, the patients were treated with 20 mg of HUMIRA SC every other week if their weight was less than 30 kg and with 40 mg of HUMIRA SC every other week if their weight was 30 kg or greater. Patients remained on stable doses of NSAIDs and or prednisone (≤0.2 mg/kg/day or 10 mg/day maximum).

Patients demonstrating a Pediatric ACR 30 response at the end of OL-LI phase were randomized into the double blind (DB) phase of the study and received either HUMIRA or placebo every other week for 32 weeks or until disease flare. Disease flare was defined as a

worsening of $\geq 30\%$ from baseline in ≥ 3 of 6 Pediatric ACR core criteria, ≥ 2 active joints, and improvement of $>30\%$ in no more than 1 of the 6 criteria. After 32 weeks or at the time of disease flare during the DB phase, patients were treated in the open-label extension phase based on the BSA regimen (OLE-BSA), before converting to a fixed dose regimen based on body weight (OLE-FD phase).

Clinical Response

At the end of the 16-week OL-LI phase, 94% of the patients in the MTX stratum and 74% of the patients in the non-MTX stratum were Pediatric ACR 30 responders. In the DB phase significantly fewer patients who received HUMIRA experienced disease flare compared to placebo, both without MTX (43% vs. 71%) and with MTX (37% vs. 65%). More patients treated with HUMIRA continued to show pediatric ACR 30/50/70 responses at Week 48 compared to patients treated with placebo. Pediatric ACR responses were maintained for up to two years in the OLE phase in patients who received HUMIRA throughout the study.

14.3 Psoriatic Arthritis

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

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

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

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

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

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

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

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

Parameter: median	Placebo N=162		HUMIRA* N=151	
	Baseline	24 weeks	Baseline	24 weeks
Number of tender joints ^a	23.0	17.0	20.0	5.0
Number of swollen joints ^b	11.0	9.0	11.0	3.0
Physician global assessment ^c	53.0	49.0	55.0	16.0
Patient global assessment ^c	49.5	49.0	48.0	20.0

Pain ^c	49.0	49.0	54.0	20.0
Disability index (HAQ) ^d	1.0	0.9	1.0	0.4
CRP (mg/dL) ^e	0.8	0.7	0.8	0.2

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

^a Scale 0-78

^b Scale 0-76

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

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

^e Normal range: 0-0.287 mg/dL

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

Radiographic Response

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

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

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

	Placebo N=141	HUMIRA N=133	
	Week 24	Week 24	Week 48
Baseline mean	22.1	23.4	23.4
Mean Change \pm SD	0.9 \pm 3.1	-0.1 \pm 1.7	-0.2 \pm 4.9*

* <0.001 for the difference between HUMIRA, Week 48 and Placebo, Week 24 (primary analysis)

Physical Function Response

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

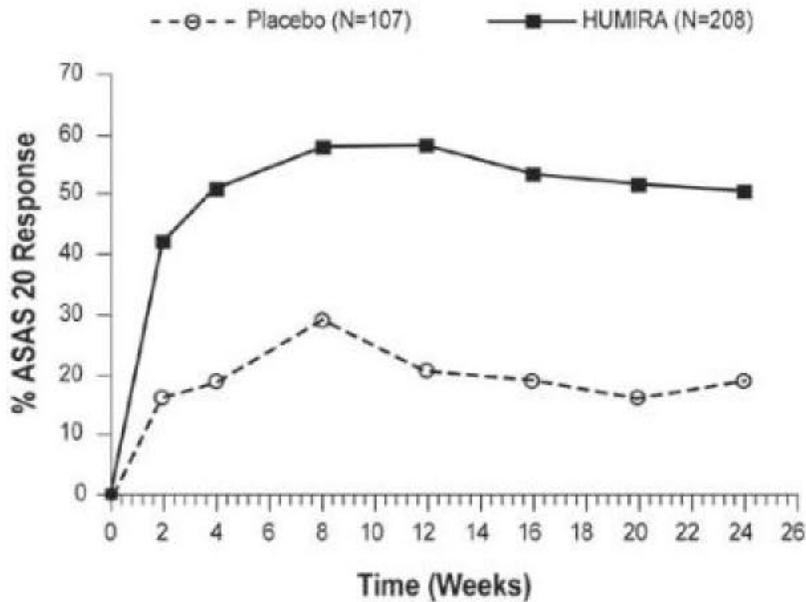
14.4 Ankylosing Spondylitis

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

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

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

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



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

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

Table 10. Components of Ankylosing Spondylitis Disease Activity

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

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

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

^c Bath Ankylosing Spondylitis Functional Index

^d Bath Ankylosing Spondylitis Disease Activity Index

^e Bath Ankylosing Spondylitis Metrology Index

^f C-Reactive Protein (mg/dL)

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

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

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

14.5 Crohn's Disease

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

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

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

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

Induction of Clinical Remission

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

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

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

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

* $p < 0.001$ for HUMIRA vs. placebo pairwise comparison of proportions

** $p < 0.01$ for HUMIRA vs. placebo pairwise comparison of proportions

Maintenance of Clinical Remission

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

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

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

Clinical remission	12%	36%*
Clinical response	18%	43%*

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

*p<0.001 for HUMIRA vs. placebo pairwise comparisons of proportions

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

14.6 Ulcerative Colitis

The safety and efficacy of HUMIRA were assessed in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12 on a 12 point scale, with an endoscopy subscore of 2 to 3 on a scale of 0 to 3) despite concurrent or prior treatment with immunosuppressants such as corticosteroids, azathioprine, or 6-MP in two randomized, double-blind, placebo-controlled clinical studies (Studies UC-I and UC-II). Both studies enrolled TNF-blocker naïve patients, but Study UC-II also allowed entry of patients who lost response to or were intolerant to TNF-blockers. Forty percent (40%) of patients enrolled in Study UC-II had previously used another TNF-blocker.

Concomitant stable doses of aminosalicylates and immunosuppressants were permitted. In Studies UC-I and II, patients were receiving aminosalicylates (69%), corticosteroids (59%) and/or azathioprine or 6-MP (37%) at baseline. In both studies, 92% of patients received at least one of these medications.

Induction of clinical remission (defined as Mayo score ≤ 2 with no individual subscores > 1) at Week 8 was evaluated in both studies. Clinical remission at Week 52 and sustained clinical remission (defined as clinical remission at both Weeks 8 and 52) were evaluated in Study UC-II.

In Study UC-I, 390 TNF-blocker naïve patients were randomized to one of three treatment groups for the primary efficacy analysis. The placebo group received placebo at Weeks 0, 2, 4 and 6. The 160/80 group received 160 mg HUMIRA at Week 0 and 80 mg at Week 2, and the 80/40 group received 80 mg HUMIRA at Week 0 and 40 mg at Week 2. After Week 2, patients in both HUMIRA treatment groups received 40 mg every other week (eow).

In Study UC-II, 518 patients were randomized to receive either HUMIRA 160 mg at Week 0, 80 mg at Week 2, and 40 mg eow starting at Week 4 through Week 50, or placebo starting at Week 0 and eow through Week 50. Corticosteroid taper was permitted starting at Week 8.

In both Studies UC-I and UC-II, a greater percentage of the patients treated with 160/80 mg of HUMIRA compared to patients treated with placebo achieved induction of clinical remission. In Study UC-II, a greater percentage of the patients treated with 160/80 mg of HUMIRA compared to patients treated with placebo achieved sustained clinical remission (clinical remission at both Weeks 8 and 52) (Table 13).

Table 13. Induction of Clinical Remission in Studies UC-I and UC-II and Sustained Clinical Remission in Study UC-II (Percent of Patients)

	Study UC-I			Study UC-II		
	Placebo N=130	HUMIRA 160/80 mg N=130	Treatment Difference (95% CI)	Placebo N=246	HUMIRA 160/80 mg N=248	Treatment Difference (95% CI)
Induction of Clinical Remission (Clinical Remission at Week 8)	9.2%	18.5%	9.3%* (0.9%, 17.6%)	9.3%	16.5%	7.2%* (1.2%, 12.9%)
Sustained Clinical Remission (Clinical Remission at both Weeks 8 and 52)	N/A	N/A	N/A	4.1%	8.5%	4.4%* (0.1%, 8.6%)

Clinical remission is defined as Mayo score ≤ 2 with no individual subscores > 1.

CI=Confidence interval

* p<0.05 for HUMIRA vs. placebo pairwise comparison of proportions

In Study UC-I, there was no statistically significant difference in clinical remission observed between the HUMIRA 80/40 mg group and the placebo group at Week 8.

In Study UC-II, 17.3% (43/248) in the HUMIRA group were in clinical remission at Week 52 compared to 8.5% (21/246) in the placebo group (treatment difference: 8.8%; 95% confidence interval (CI): [2.8%, 14.5%]; p<0.05).

In the subgroup of patients in Study UC-II with prior TNF-blocker use, the treatment difference for induction of clinical remission appeared to be lower than that seen in the whole study population, and the treatment differences for sustained clinical remission and clinical remission at Week 52 appeared to be similar to those seen in the whole study population. The subgroup of patients with prior TNF-blocker use achieved induction of clinical remission at 9% (9/98) in the HUMIRA group versus 7% (7/101) in the placebo group, and sustained clinical remission at 5% (5/98) in the HUMIRA group versus 1% (1/101) in the placebo group. In the subgroup of patients with prior TNF-blocker use, 10% (10/98) were in clinical remission at Week 52 in the HUMIRA group versus 3% (3/101) in the placebo group.

14.7 Plaque Psoriasis

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

Study Ps-I evaluated 1212 patients with chronic Ps with $\geq 10\%$ body surface area (BSA) involvement, Physician's Global Assessment (PGA) of at least moderate disease severity, and Psoriasis Area and Severity Index (PASI) ≥ 12 within three treatment periods. In period A, patients received placebo or HUMIRA at an initial dose of 80 mg at Week 0 followed by a dose of 40 mg every other week starting at Week 1. After 16 weeks of therapy, patients who achieved at least a PASI 75 response at Week 16, defined as a PASI score improvement of at least 75% relative to baseline, entered period B and received open-label 40 mg HUMIRA every other week. After 17 weeks of open label therapy, patients who maintained at least a PASI 75 response at Week 33 and were originally randomized to active therapy in period A were re-randomized in period C to receive 40 mg HUMIRA every other week or placebo for an additional 19 weeks. Across all treatment groups the mean baseline PASI score was 19 and the baseline Physician's Global Assessment score ranged from "moderate" (53%) to "severe" (41%) to "very severe" (6%).

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

Studies Ps-I and II evaluated the proportion of patients who achieved "clear" or "minimal" disease on the 6-point PGA scale and the proportion of patients who achieved a reduction in PASI score of at least 75% (PASI 75) from baseline at Week 16 (see Table 14 and 15).

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

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

	HUMIRA 40 mg every other week N = 814	Placebo N = 398
PGA: Clear or minimal*	506 (62%)	17 (4%)
PASI 75	578 (71%)	26 (7%)

* Clear = no plaque elevation, no scale, plus or minus hyperpigmentation or diffuse pink or red coloration

Minimal = possible but difficult to ascertain whether there is slight elevation of plaque above normal skin, plus or minus surface dryness with some white coloration, plus or minus up to red coloration

Table 15. Efficacy Results at 16 Weeks in Study Ps-II Number of Patients (%)

	HUMIRA 40 mg every other week N = 99	Placebo N = 48
PGA: Clear or minimal*	70 (71%)	5 (10%)
PASI 75	77 (78%)	9 (19%)

* Clear = no plaque elevation, no scale, plus or minus hyperpigmentation or diffuse pink or red coloration

Minimal = possible but difficult to ascertain whether there is slight elevation of plaque above normal skin, plus or minus surface dryness with some white coloration, plus or minus up to red coloration

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

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

15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

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

• HUMIRA Pen Carton

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

• HUMIRA Pen – Crohn's Disease/Ulcerative Colitis Starter Package

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

• HUMIRA Pen – Psoriasis Starter Package

HUMIRA is dispensed in a carton containing 4 alcohol preps and 4 dose trays (Psoriasis Starter Package). Each dose tray consists of a single-use pen, containing a 1 mL prefilled glass syringe with a fixed 27 gauge ½ inch needle, providing 40 mg (0.8 mL) of HUMIRA. The NDC number is 0074-4339-07.

• Prefilled Syringe Carton – 40 mg

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

• Pediatric Prefilled Syringe Carton – 20 mg

HUMIRA is supplied for pediatric use only in a carton containing two alcohol preps and two dose trays. Each dose tray consists of a single-use, 1 mL pre-filled glass syringe with a fixed 27 gauge ½ inch needle, providing 20 mg (0.4 mL) of HUMIRA. The NDC number is 0074-9374-02.

• Institutional Use Vial Carton – 40 mg

HUMIRA is supplied for institutional use only in a carton containing a single-use, glass vial, providing 40 mg (0.8 mL) of HUMIRA. The NDC number is 0074-3797-01.

Storage and Stability

Do not use beyond the expiration date on the container. HUMIRA must be refrigerated at 36°F to 46°F (2°C to 8°C). DO NOT FREEZE. Do not use if frozen even if it has been thawed. When traveling, store HUMIRA in a cool carrier with an ice pack. Protect the prefilled syringe from exposure to light. Store in original carton until time of administration.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide and Instructions for Use).

17.1 Patient Counseling

Provide the HUMIRA “Medication Guide” to patients or their caregivers, and provide them an opportunity to read it and ask questions prior to initiation of therapy and prior to each time the prescription is renewed. If patients develop signs and symptoms of infection, instruct them to seek medical evaluation immediately.

Advise patients of the potential benefits and risks of HUMIRA.

• Infections

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

• Malignancies

Counsel patients about the risk of malignancies while receiving HUMIRA.

• Allergic Reactions

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

• **Other Medical Conditions**

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

17.2 Instruction on Injection Technique

Inform patients that the first injection is to be performed under the supervision of a qualified health care professional. If a patient or caregiver is to administer HUMIRA, instruct them in injection techniques and assess their ability to inject subcutaneously to ensure the proper administration of HUMIRA [see *Instructions for Use*].

For patients who will use the HUMIRA Pen, tell them that they:

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

Instruct patients to dispose of their used needles and syringes or used Pen in a FDA-cleared sharps disposal container immediately after use. **Instruct patients not to dispose of loose needles and syringes or Pen in their household trash.** Instruct patients that if they do not have a FDA-cleared sharps disposal container, they may use a household container that is made of a heavy-duty plastic, can be closed with a tight-fitting and puncture-resistant lid without sharps being able to come out, upright and stable during use, leak-resistant, and properly labeled to warn of hazardous waste inside the container.

Instruct patients that when their sharps disposal container is almost full, they will need to follow their community guidelines for the correct way to dispose of their sharps disposal container. Instruct patients that there may be state or local laws regarding disposal of used needles and syringes. Refer patients to the FDA’s website at <http://www.fda.gov/safesharpsdisposal> for more information about safe sharps disposal, and for specific information about sharps disposal in the state that they live in.

Instruct patients not to dispose of their used sharps disposal container in their household trash unless their community guidelines permit this. Instruct patients not to recycle their used sharps disposal container.

AbbVie Inc.

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

MEDICATION GUIDE

HUMIRA® (Hu-MARE-ah)

(adalimumab)

injection

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

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

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

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

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

Before starting HUMIRA, tell your doctor if you:

- think you have an infection or have symptoms of infection such as:
 - fever, sweats, or chills
 - muscle aches
 - cough
 - shortness of breath
 - blood in phlegm
 - weight loss
 - warm, red, or painful skin or sores on your body
 - diarrhea or stomach pain
 - burning when you urinate or urinate more often than normal
 - feel very tired
- are being treated for an infection
- get a lot of infections or have infections that keep coming back
- have diabetes
- have TB, or have been in close contact with someone with TB

- were born in, lived in, or traveled to countries where there is more risk for getting TB. Ask your doctor if you are not sure.
- live or have lived in certain parts of the country (such as the Ohio and Mississippi River valleys) where there is an increased risk for getting certain kinds of fungal infections (histoplasmosis, coccidioidomycosis, or blastomycosis). These infections may happen or become more severe if you use HUMIRA. Ask your doctor if you do not know if you have lived in an area where these infections are common.
- have or have had hepatitis B
- use the medicine ORENCIA[®] (abatacept), KINERET[®] (anakinra), RITUXAN[®] (rituximab), IMURAN[®] (azathioprine), or PURINETHOL[®] (6-mercaptopurine, 6-MP).
- are scheduled to have major surgery

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

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

Cancer

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

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

What is HUMIRA?

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

- To reduce the signs and symptoms of:
- **moderate to severe rheumatoid arthritis (RA) in adults.** HUMIRA can be used alone, with methotrexate, or with certain other medicines.
- **moderate to severe polyarticular juvenile idiopathic arthritis (JIA) in children** 4 years and older. HUMIRA can be used alone, with methotrexate, or with certain other medicines.
- **psoriatic arthritis (PsA) in adults.** HUMIRA can be used alone or with certain other medicines.
- **ankylosing spondylitis (AS) in adults.**
- **moderate to severe Crohn's disease (CD) in adults** when other treatments have not worked well enough.
- In adults, to help get **moderate to severe ulcerative colitis (UC)** under control (induce remission) and keep it under control (sustain remission) when certain other medicines have not worked well enough. It is not known if HUMIRA is effective in people who stopped responding to or could not tolerate TNF-blocker medicines.
- **To treat moderate to severe chronic (lasting a long time) plaque psoriasis (Ps) in adults** who have the condition in many areas of their body and who may benefit from taking injections or pills (systemic therapy) or phototherapy (treatment using ultraviolet light alone or with pills).

What should I tell my doctor before taking HUMIRA?

HUMIRA may not be right for you. Before starting HUMIRA, tell your doctor about all of your health conditions, including if you:

- have an infection. See **"What is the most important information I should know about HUMIRA?"**
- have or have had cancer.
- have any numbness or tingling or have a disease that affects your nervous system such as multiple sclerosis or Guillain-Barré syndrome.

- have or had heart failure.
 - have recently received or are scheduled to receive a vaccine. You may receive vaccines, except for live vaccines while using HUMIRA. Children with juvenile idiopathic arthritis should be brought up to date with all vaccines before starting HUMIRA.
 - are allergic to rubber or latex. The needle cover on the prefilled syringe contains dry natural rubber. Tell your doctor if you have any allergies to rubber or latex.
 - are allergic to HUMIRA or to any of its ingredients. See the end of this Medication Guide for a list of ingredients in HUMIRA.
 - are pregnant or planning to become pregnant. It is not known if HUMIRA will harm your unborn baby. HUMIRA should only be used during a pregnancy if needed.
- Pregnancy Registry:** AbbVie Inc. has a registry for pregnant women who take HUMIRA. The purpose of this registry is to check the health of the pregnant mother and her child. Talk to your doctor if you are pregnant and contact the registry at 1-877-311-8972.
- breastfeeding or plan to breastfeed. You and your doctor should decide if you will breastfeed or use HUMIRA. You should not do both.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Especially tell your doctor if you use:

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

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

How should I take HUMIRA?

- HUMIRA is given by an injection under the skin. Your doctor will tell you how often to take an injection of HUMIRA. This is based on your condition to be treated. **Do not inject HUMIRA more often than you were prescribed.**
- See the **Instructions for Use** inside the carton for complete instructions for the right way to prepare and inject HUMIRA.
- Make sure you have been shown how to inject HUMIRA before you do it yourself. You can call your doctor or 1-800-4HUMIRA (1-800-448-6472) if you have any questions about giving yourself an injection. Someone you know can also help you with your injection after he/she has been shown how to prepare and inject HUMIRA.
- **Do not** try to inject HUMIRA yourself until you have been shown the right way to give the injections. If your doctor decides that you or a caregiver may be able to give your injections of HUMIRA at home, you should receive training on the right way to prepare and inject HUMIRA.
- Do not miss any doses of HUMIRA unless your doctor says it is okay. If you forget to take HUMIRA, inject a dose as soon as you remember. Then, take your next dose at your regular scheduled time. This will put you back on schedule. In case you are not sure when to inject HUMIRA, call your doctor or pharmacist.
- If you take more HUMIRA than you were told to take, call your doctor.

What are the possible side effects of HUMIRA?

HUMIRA can cause serious side effects, including:

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

• **Serious Infections.**

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

- cough that does not go away
- low grade fever
- weight loss

- loss of body fat and muscle (wasting)

- **Hepatitis B infection in people who carry the virus in their blood.**

If you are a carrier of the hepatitis B virus (a virus that affects the liver), the virus can become active while you use HUMIRA. Your doctor should do blood tests before you start treatment, while you are using HUMIRA, and for several months after you stop treatment with HUMIRA. Tell your doctor if you have any of the following symptoms of a possible hepatitis B infection:

- muscle aches
- feel very tired
- dark urine
- skin or eyes look yellow
- little or no appetite
- vomiting
- clay-colored bowel movements
- fever
- chills
- stomach discomfort
- skin rash

- **Allergic reactions.** Allergic reactions can happen in people who use HUMIRA. Call your doctor or get medical help right away if you have any of these symptoms of a serious allergic reaction:

- hives
- swelling of your face, eyes, lips or mouth
- trouble breathing

- **Nervous system problems.** Signs and symptoms of a nervous system problem include: numbness or tingling, problems with your vision, weakness in your arms or legs, and dizziness.

- **Blood problems.** Your body may not make enough of the blood cells that help fight infections or help to stop bleeding. Symptoms include a fever that does not go away, bruising or bleeding very easily, or looking very pale.

- **New heart failure or worsening of heart failure you already have. Call your doctor right away** if you get new worsening symptoms of heart failure while taking HUMIRA, including:

- shortness of breath
- swelling of your ankles or feet
- sudden weight gain.

- **Immune reactions including a lupus-like syndrome.** Symptoms include chest discomfort or pain that does not go away, shortness of breath, joint pain, or a rash on your cheeks or arms that gets worse in the sun. Symptoms may improve when you stop HUMIRA.

- **Liver Problems.** Liver problems can happen in people who use TNF-blocker medicines. These problems can lead to liver failure and death. Call your doctor right away if you have any of these symptoms:

- feel very tired
- skin or eyes look yellow
- poor appetite or vomiting
- pain on the right side of your stomach (abdomen)

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

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

Common side effects with HUMIRA include:

- injection site reactions: redness, rash, swelling, itching, or bruising. These symptoms usually will go away within a few days. Call your doctor right away if you have pain, redness or swelling around the injection site that does not go away within a few days or gets worse.
- upper respiratory infections (including sinus infections)
- headaches
- rash
- nausea

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

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

How should I store HUMIRA?

- Store HUMIRA in a refrigerator at 36°F to 46°F (2°C to 8°C) in the original container until it is used. Protect from light.
- When traveling, HUMIRA should be stored in a cool carrier with an ice pack.
- **Do not freeze HUMIRA.** Do not use HUMIRA if frozen, even if it has been thawed.
- Refrigerated HUMIRA may be used until the expiration date printed on the HUMIRA carton, dose tray, Pen or prefilled syringe.
- Do not use a Pen or prefilled syringe if the liquid is cloudy, discolored, or has flakes or particles in it.
- Do not drop or crush HUMIRA. The prefilled syringe is glass.
- **Keep HUMIRA, injection supplies, and all other medicines out of the reach of children.**

General information about HUMIRA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use HUMIRA for a condition for which it was not prescribed. Do not give HUMIRA to other people, even if they have the same condition. It may harm them. This Medication Guide summarizes the most important information about HUMIRA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about HUMIRA that was written for healthcare professionals. For more information go to www.HUMIRA.com or you can enroll in a patient support program by calling 1-800-4HUMIRA (1-800-448-6472).

What are the ingredients in HUMIRA?

Active ingredient: adalimumab

Inactive ingredients: sodium chloride, monobasic sodium phosphate dihydrate, dibasic sodium phosphate dihydrate, sodium citrate, citric acid monohydrate, mannitol, polysorbate 80, and Water for Injection. Sodium hydroxide is added as necessary to adjust pH. This Medication Guide has been approved by the U.S. Food and Drug Administration.

AbbVie Inc.

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

Content revised 01/2013

INSTRUCTIONS FOR USE

HUMIRA® (Hu-MARE-ah)

(adalimumab)

SINGLE-USE PEN

Do not try to inject HUMIRA yourself until you have been shown the right way to give the injections. If your doctor decides that you or a caregiver may be able to give your injections of HUMIRA at home, you should receive training on the right way to prepare and inject HUMIRA. It is important that you read, understand, and follow these instructions so that you inject HUMIRA the right way. Call your healthcare provider if you or your caregiver has any questions about the right way to inject HUMIRA.

IMPORTANT:

- Do not use HUMIRA if frozen, even if it has been thawed.
- The HUMIRA Pen contains glass. Do not drop or crush the Pen because the glass inside may break.
- Do not remove the gray cap or the plum-colored cap until right before your injection.
- When the plum-colored button on the HUMIRA Pen is pressed to give your dose of HUMIRA, you will hear a loud “click” sound.
- You must practice injecting HUMIRA with your doctor or nurse so that you are not startled by this click when you start giving yourself the injections at home.
- The loud click sound means the start of the injection.
- You will know that the injection has finished when the yellow marker appears fully in the window view and stops moving.

See the section below called “**Prepare the HUMIRA Pen**”.

How should I store HUMIRA?

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

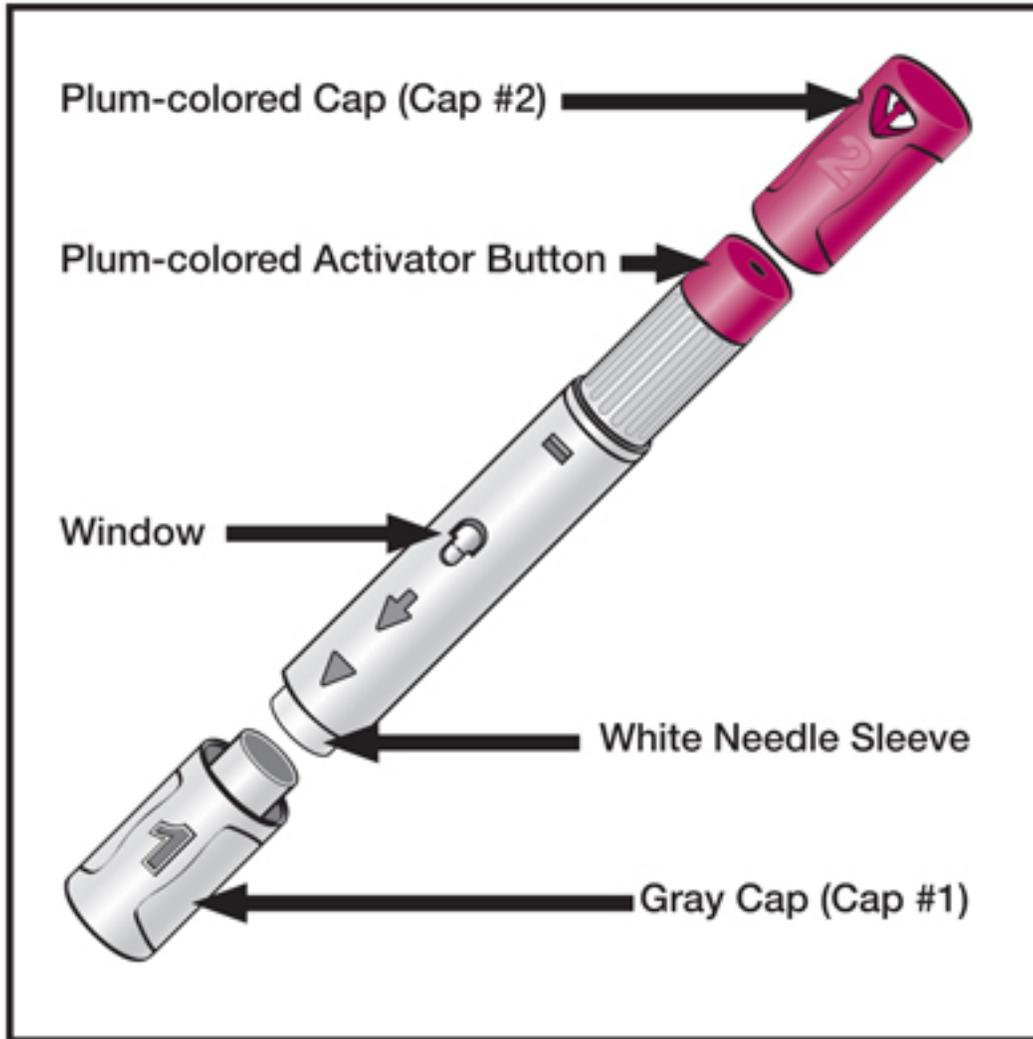
- Do not drop or crush HUMIRA.
- **Keep HUMIRA, injection supplies, and all other medicines out of the reach of children.**

Gather the Supplies for Your Injection

- You will need the following supplies for your injection of HUMIRA.
 - Find a clean, flat surface to place the supplies on.
- 1 alcohol swab
- 1 cotton ball or gauze pad (not included in your HUMIRA carton)
- 1 HUMIRA Pen (See Figure A)
- 1 FDA-cleared sharps disposal container for HUMIRA Pen disposal (not included in your HUMIRA carton)

If you do not have all of the supplies you need to give yourself an injection, go to a pharmacy or call your pharmacist. The diagram below shows what the HUMIRA Pen looks like. See Figure A.

Figure A

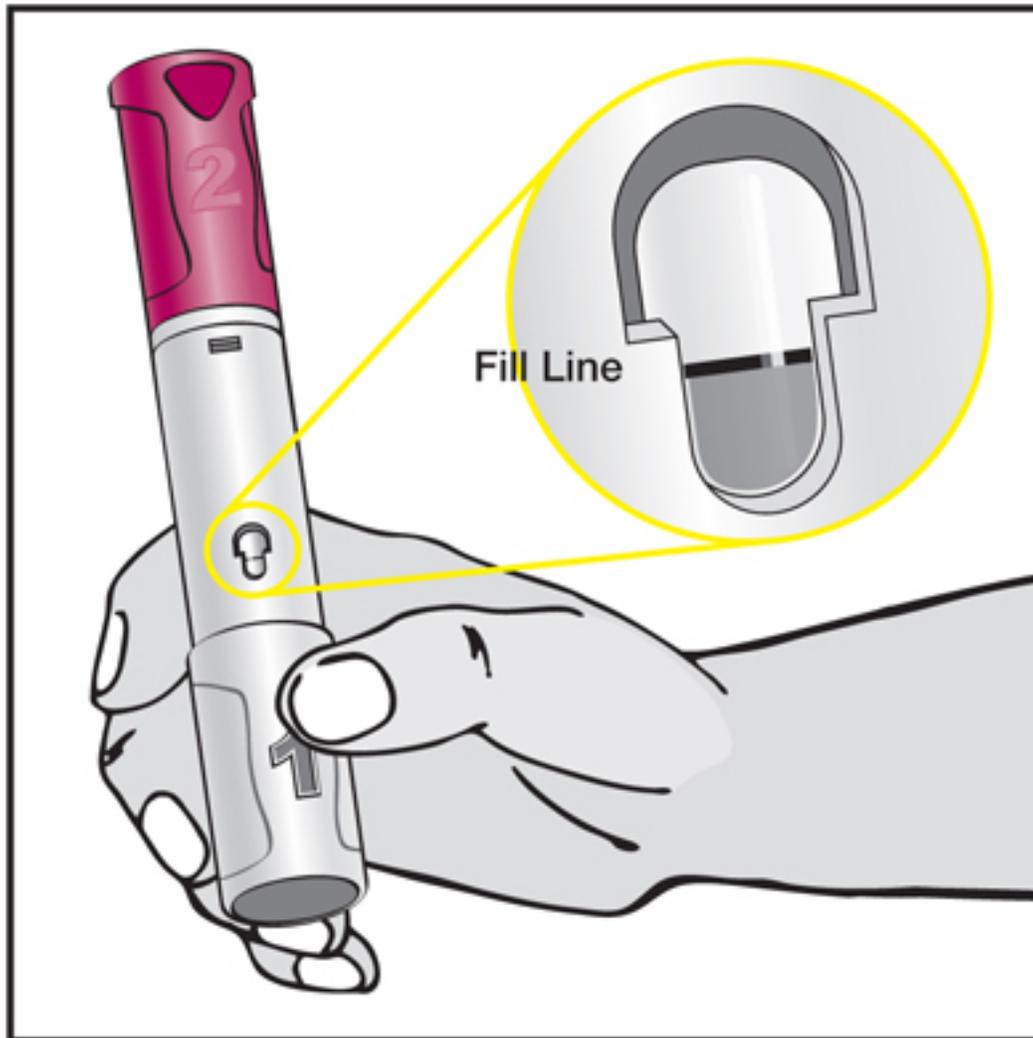


Check the carton, dose tray, and HUMIRA Pen.

1. Make sure the name HUMIRA appears on the carton, dose tray, and HUMIRA Pen label.
2. **Do not** use and call your doctor or pharmacist if:
 - you drop or crush your HUMIRA Pen.
 - the seals on the top or bottom of the carton are broken or missing.
 - the expiration date on the carton, dose tray, and Pen has passed.
 - the HUMIRA Pen has been frozen or left in direct sunlight. See the section: **“How should I store HUMIRA?”** at the beginning of these Instructions For Use.

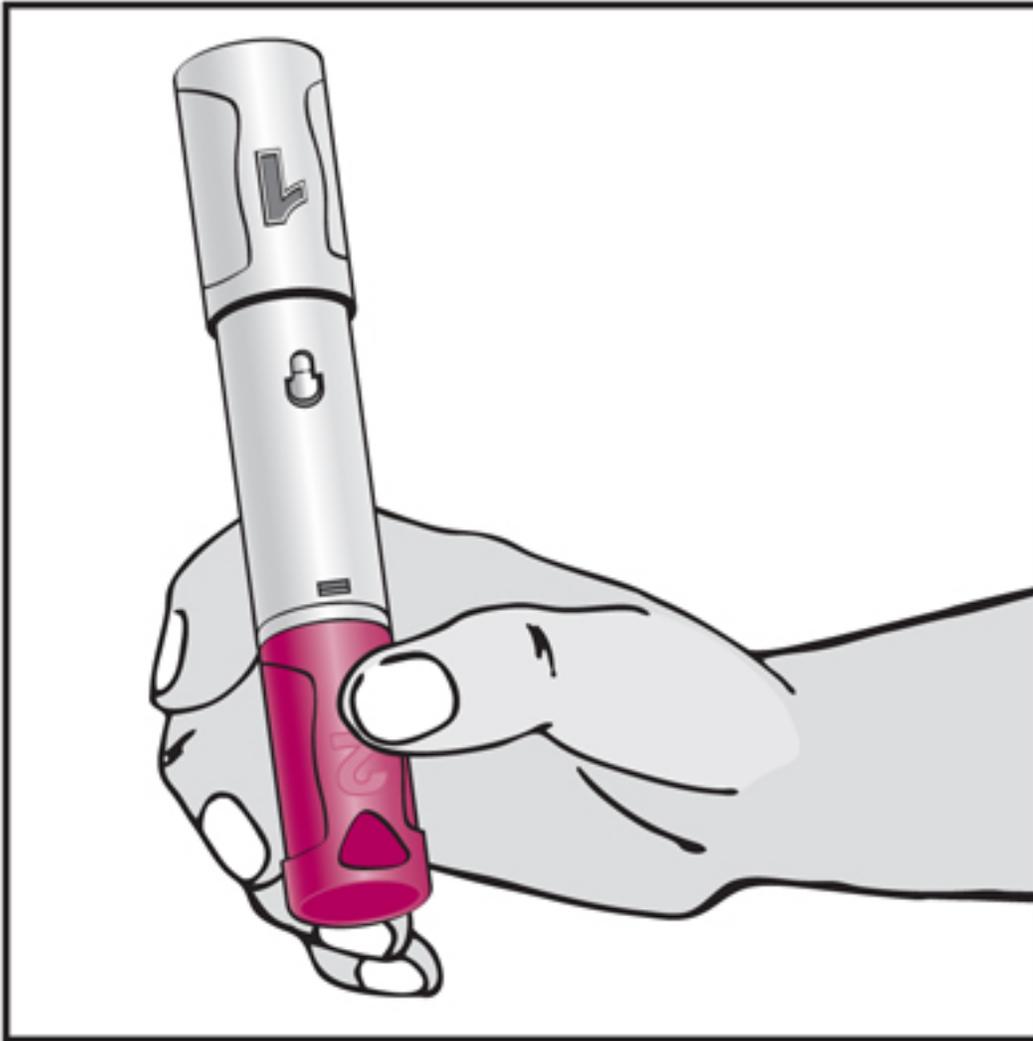
3. Hold the Pen with the gray cap (Cap # 1) pointed down.
4. Make sure the amount of liquid in the Pen is at the fill line or close to the fill line seen through the window. This is the full dose of HUMIRA that you will inject. See Figure B.
5. If the Pen does not have the full amount of liquid, **do not use that Pen**. Call your pharmacist.

Figure B



6. Turn the Pen over and hold the Pen with the gray cap (Cap # 1) pointed up. See Figure C.
7. Check the solution through the windows on the side of the Pen to make sure the liquid is clear and colorless. **Do not use** your HUMIRA Pen if the liquid is cloudy, discolored, or if it has flakes or particles in it. Call your pharmacist. It is normal to see one or more bubbles in the window.

Figure C



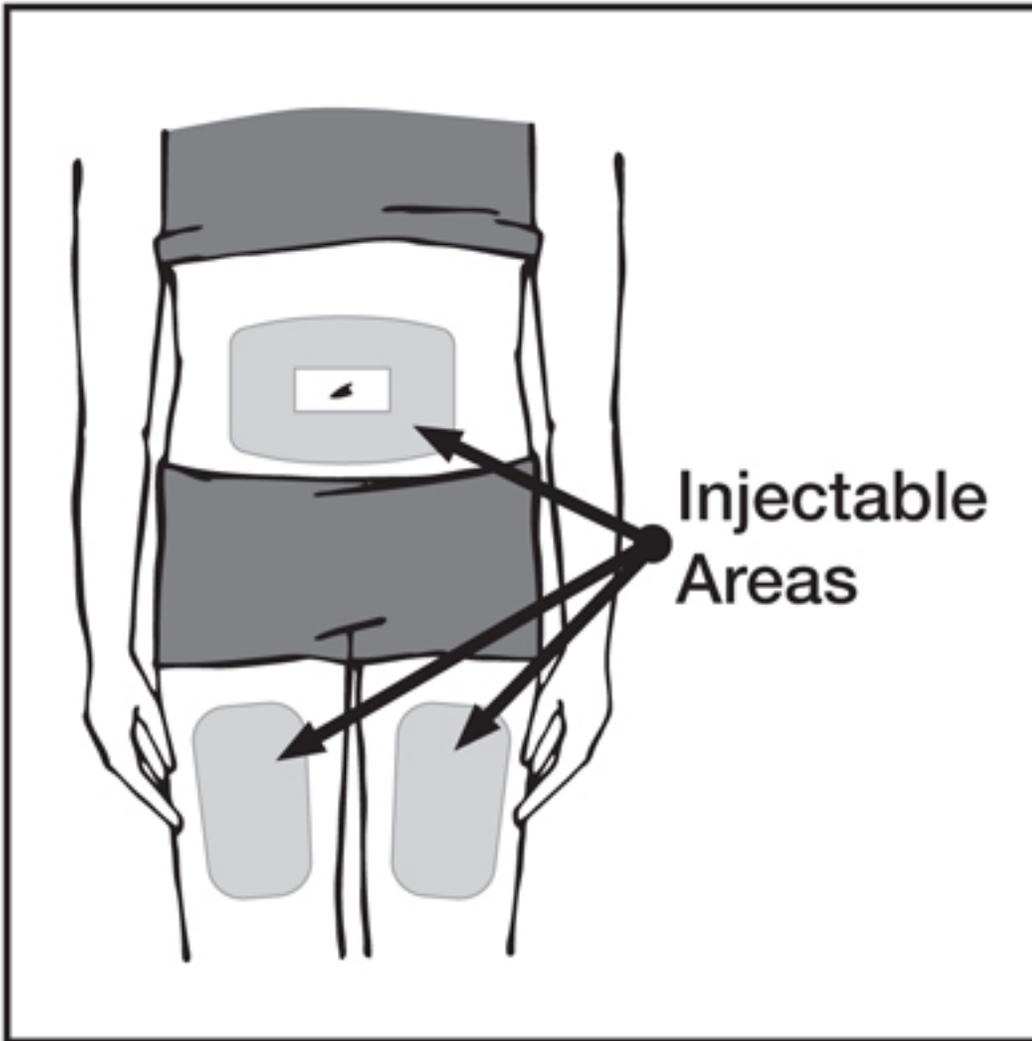
Choose the Injection Site

8. Wash and dry your hands well.

9. Choose an injection site on:

- the front of your thighs or
- your lower abdomen (belly). If you choose your abdomen, do not use the area 2 inches around your belly button (navel). See Figure D.

Figure D



- 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 HUMIRA into skin that is:
 - sore (tender)
 - bruised
 - red
 - hard
 - scarred or where you have stretch marks
- If you have psoriasis, **do not** inject directly into any raised, thick, red or scaly skin patches or lesions on your skin.
- Do not inject through your clothes.

Prepare the Injection Site

10. Wipe the injection site with an alcohol prep (swab) using a circular motion.

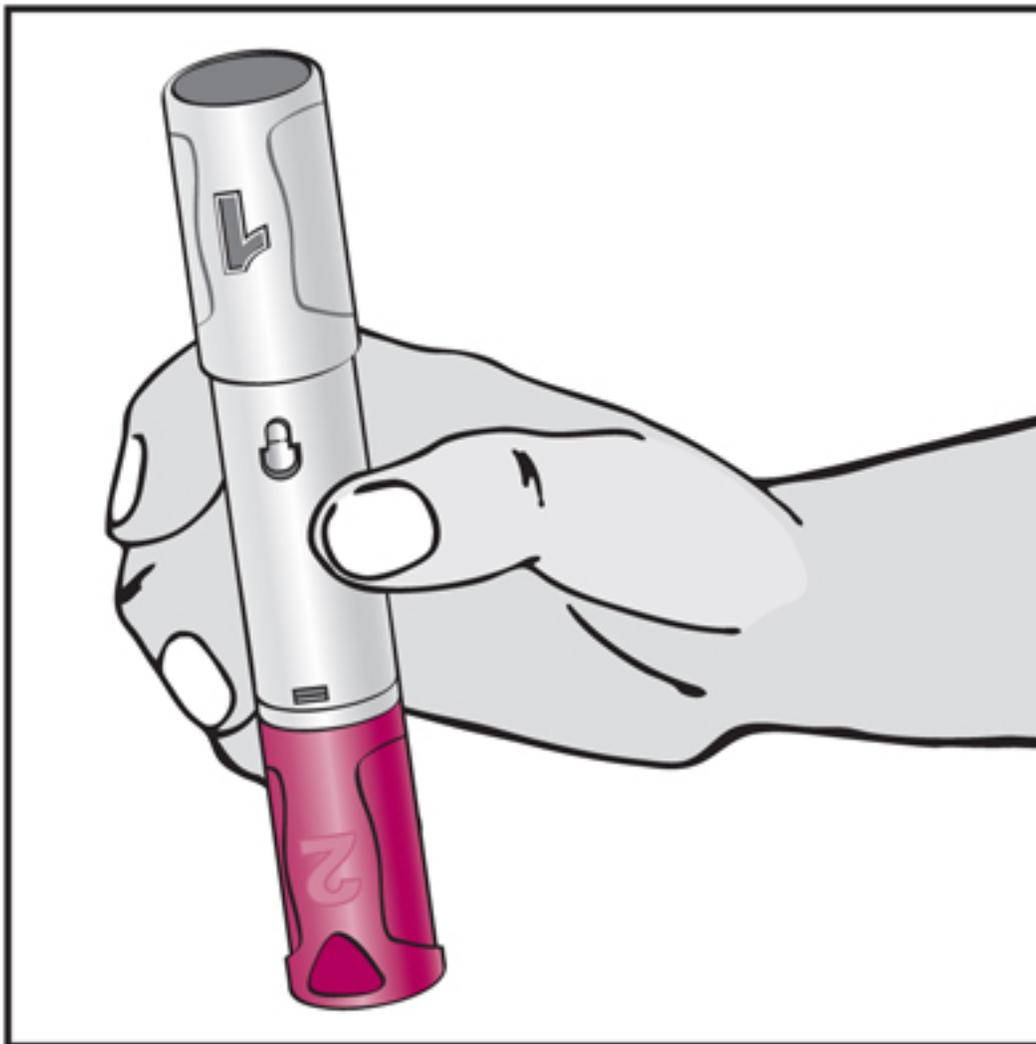
- **Do not** touch this area again before giving the injection. Allow the skin to dry before injecting. **Do not** fan or blow on the clean area.

Preparing the HUMIRA Pen

11. **Do not remove the gray cap (Cap # 1) or the plum-colored cap (Cap # 2) until right before your injection.**

12. Hold the middle of the Pen (gray body) with one hand so that you are not touching the gray cap (Cap # 1) or the plum-colored cap (Cap # 2). Turn the Pen so that the gray cap (Cap # 1) is pointing up. See Figure E.

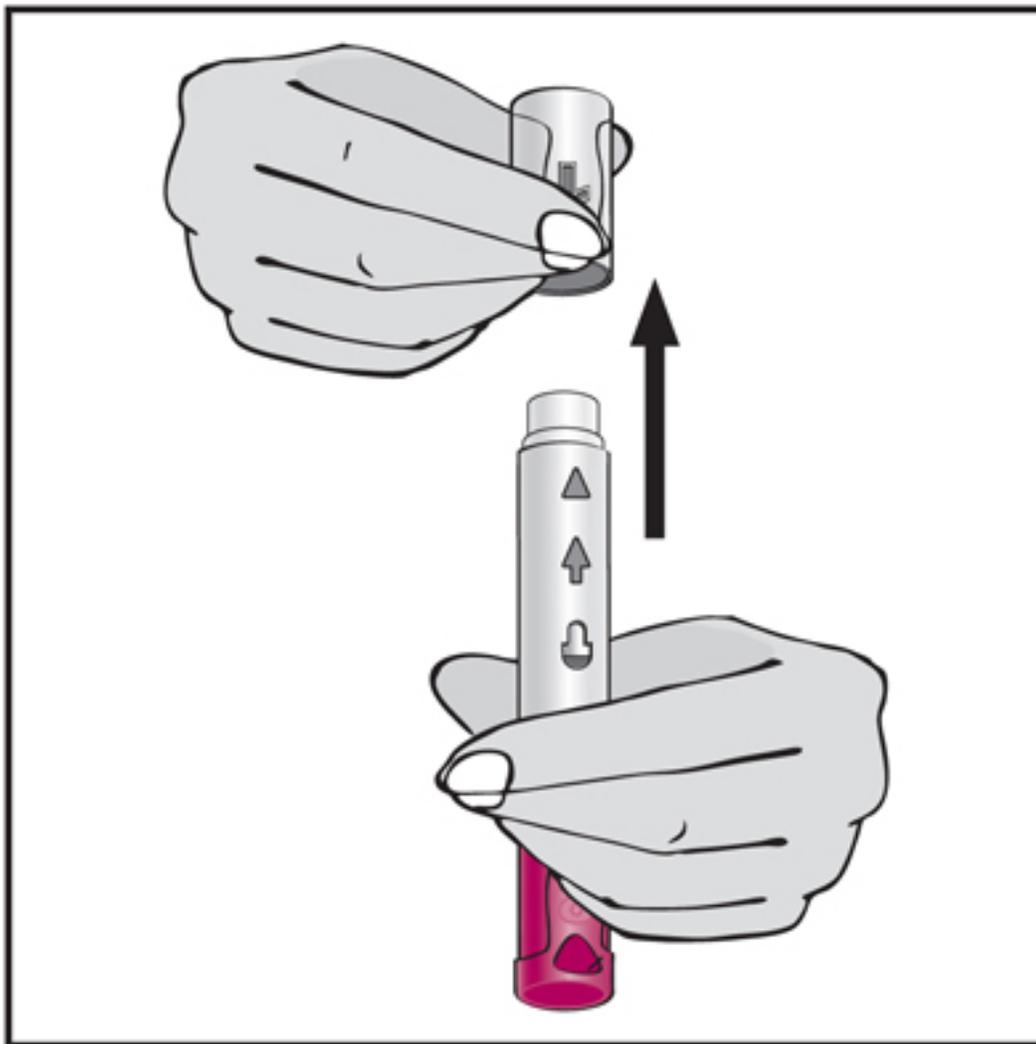
Figure E



13. With your other hand, pull the gray cap (Cap # 1) straight off (do not twist the cap). Make sure the small gray needle cover of the syringe has come off with the gray cap (Cap # 1). See Figure F.

14. Throw away the gray cap (Cap # 1).

Figure F



- **Do not** put the gray cap (Cap # 1) back on the Pen. Putting the gray cap (Cap # 1) back on may damage the needle.
- The white needle sleeve, which covers the needle, can now be seen.
- **Do not** touch the needle with your fingers or let the needle touch anything.
- You may see a few drops of liquid come out of the needle. This is normal.

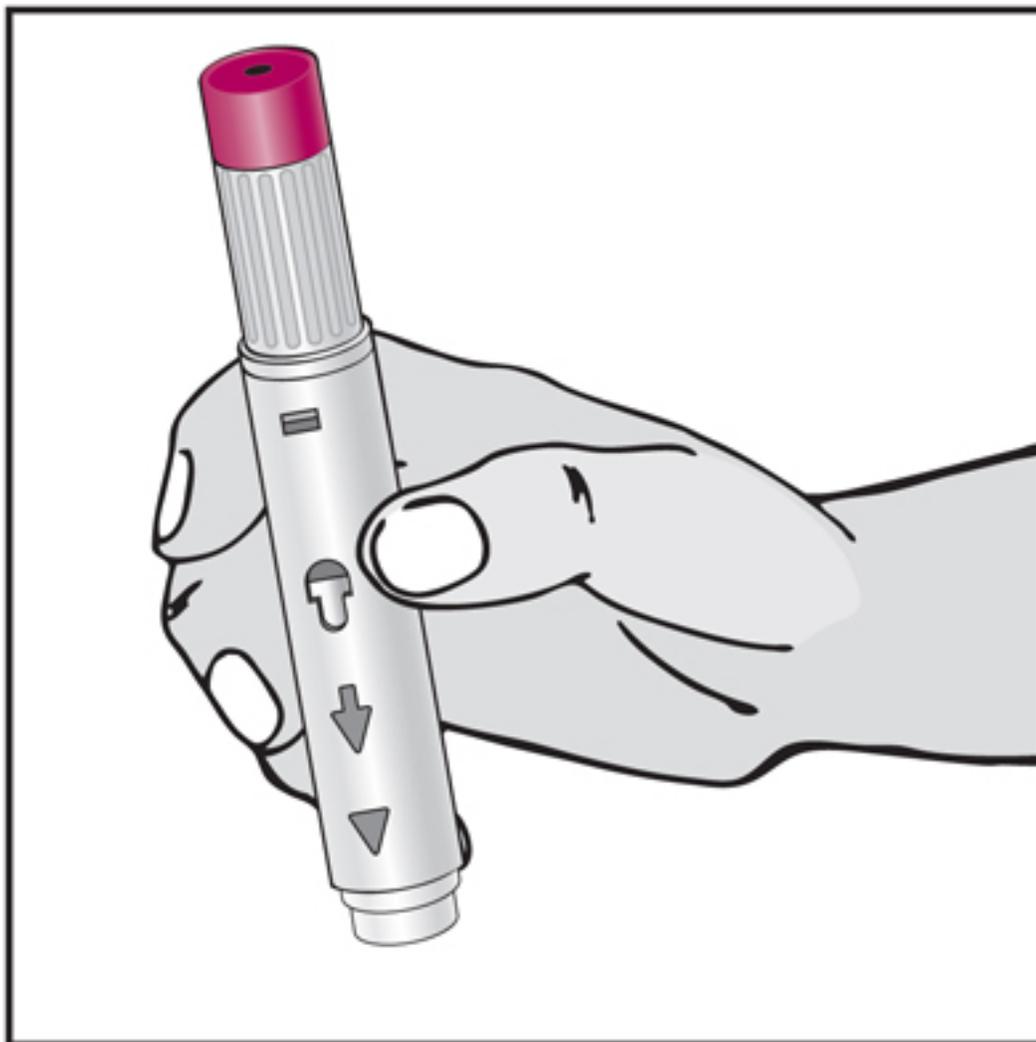
15. Remove the plum-colored cap (Cap # 2) from the bottom of the Pen by pulling it straight off (do not twist the cap). The Pen is now activated. Throw away the plum-colored cap.

- Do not put the plum-colored cap (Cap # 2) back on the Pen because it could cause medicine to come out of the syringe.

The plum-colored activator button:

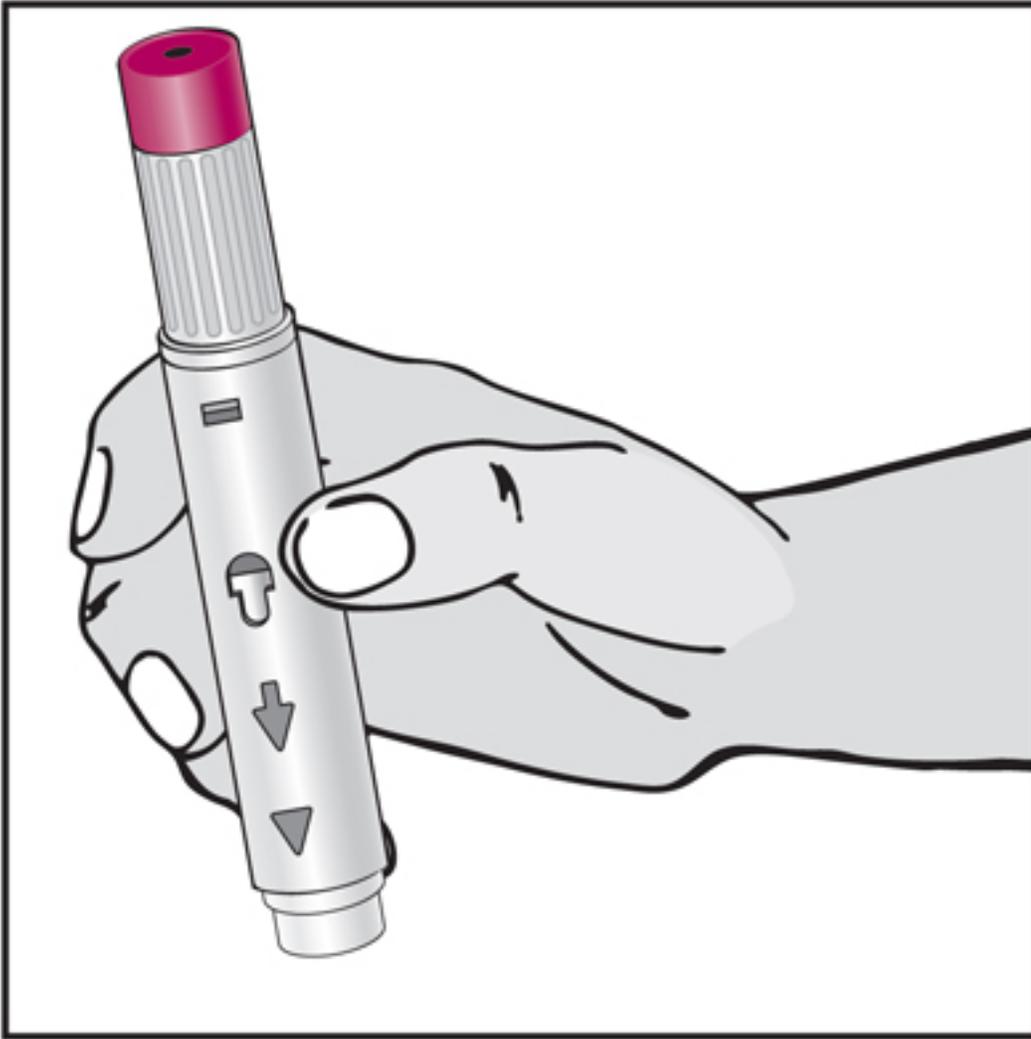
- Turn the Pen so the plum-colored activator button is pointed up. See Figure G.

Figure G



- **Do not** press the plum-colored activator button until you are ready to inject HUMIRA. Pressing the plum-colored activator button will release the medicine from the Pen.
- Hold the Pen so that you can see the window. See Figure H. It is normal to see one or more bubbles in the window.

Figure H



Position the Pen and Inject HUMIRA

16. Position the Pen:

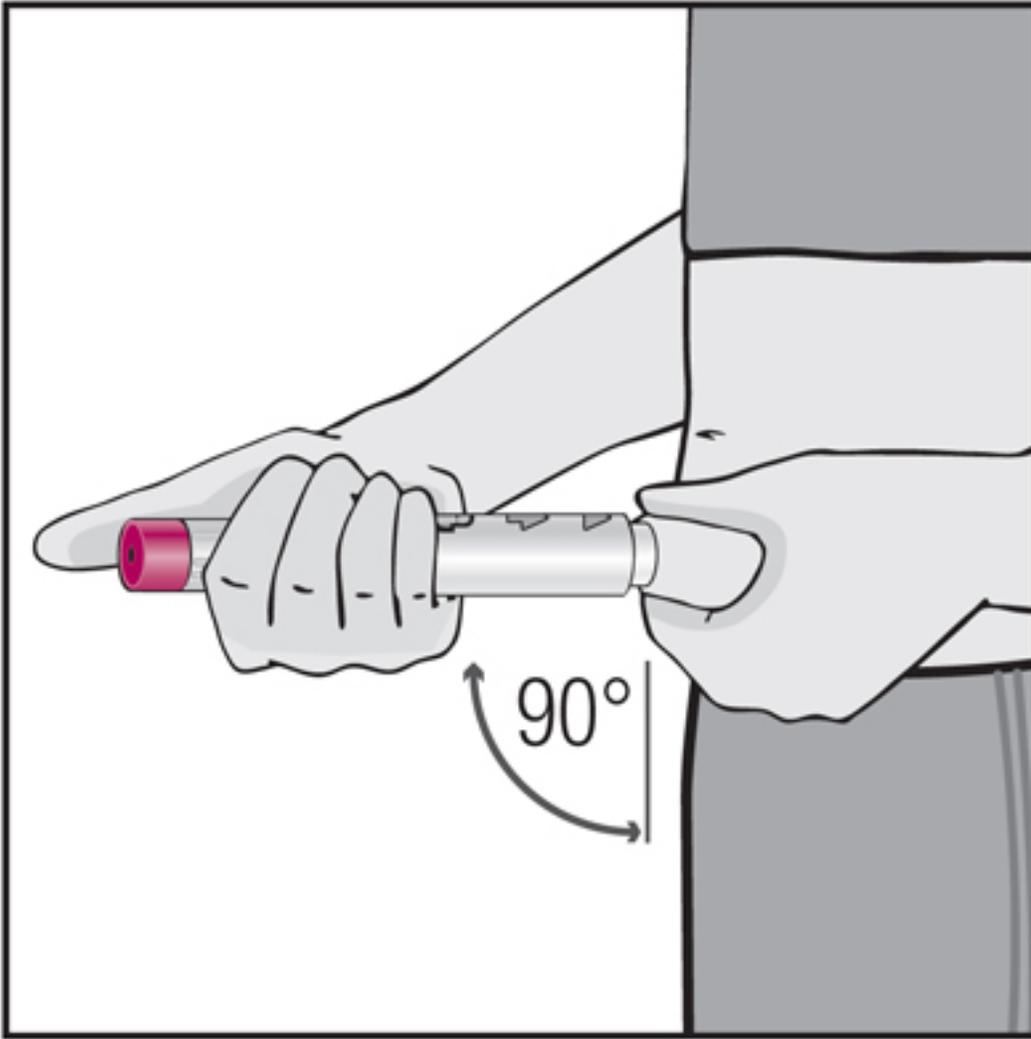
- Gently squeeze the area of the cleaned skin and hold it firmly. See Figure I. You will inject into this raised area of skin.

Figure I



17. Place the white end of the Pen straight (at a 90° angle) and flat against the raised area of your skin that you are squeezing. Place the Pen so that it will not inject the needle into your fingers that are holding the raised skin. See Figure J.

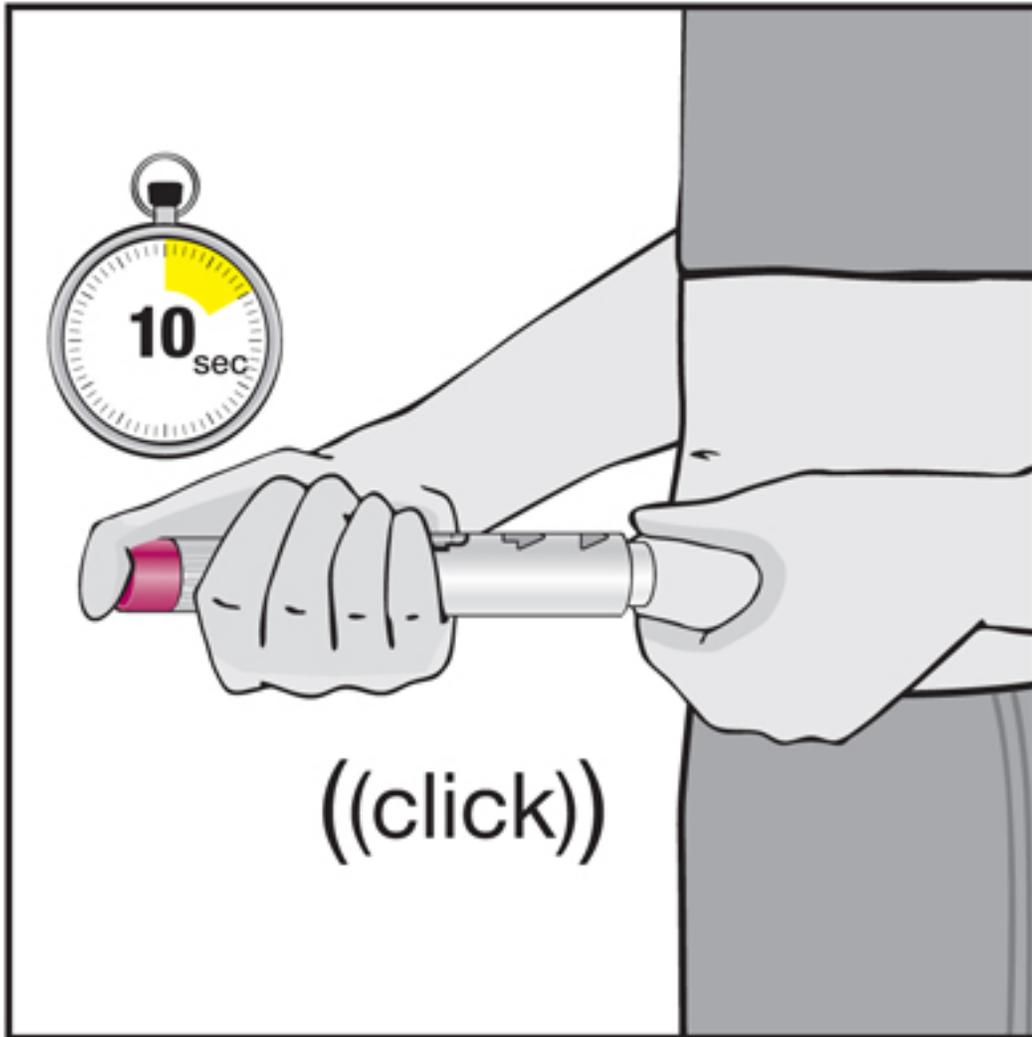
Figure J



18. Inject HUMIRA

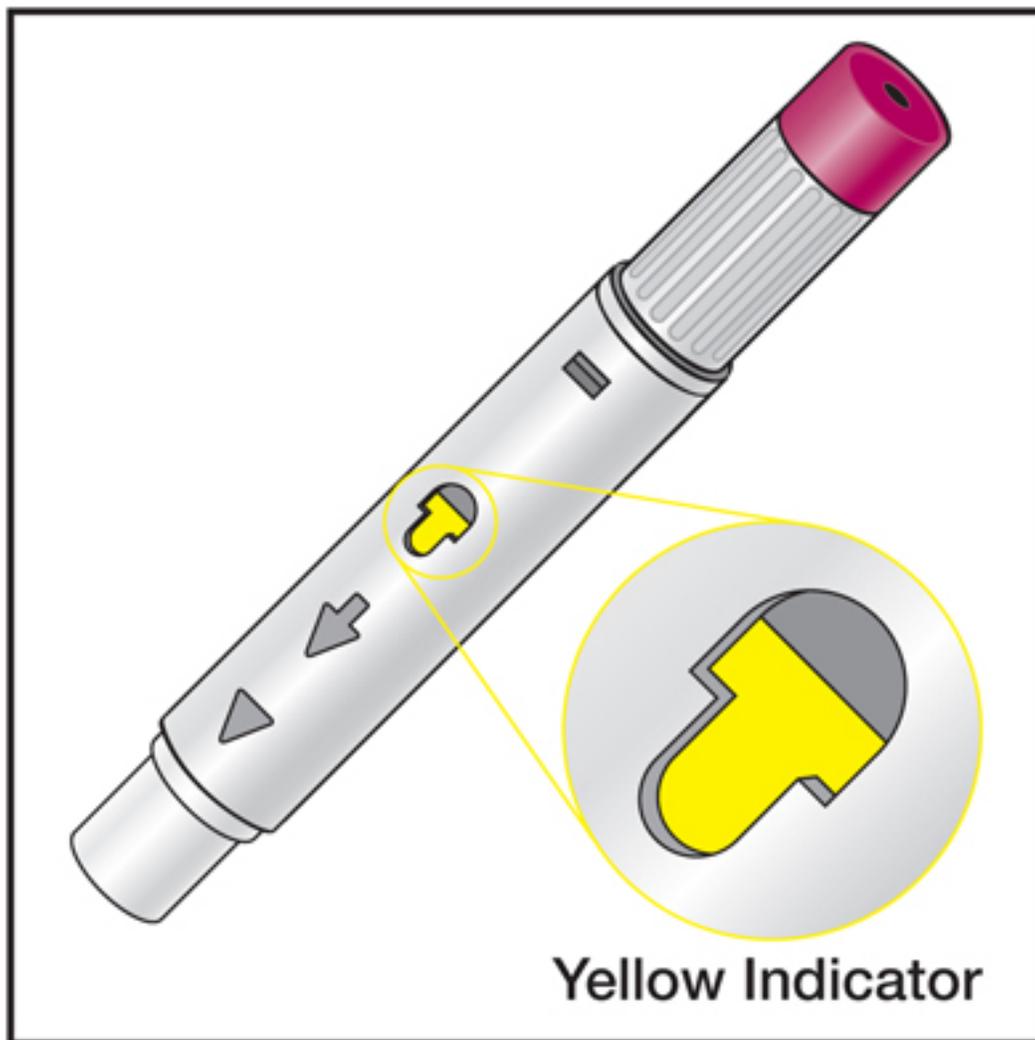
- With your index finger or your thumb, press the plum-colored activator button to begin the injection. Try not to cover the window. See Figure K.

Figure K



- You will hear a loud 'click' when you press the plum-colored activator button. The loud click means the start of the injection.
- Keep pressing the plum-colored activator button and continue to hold the Pen against your squeezed, raised skin until all of the medicine is injected. This can take up to 10 seconds, so count slowly to ten. Keep holding the Pen against the squeezed, raised skin of your injection site for the whole time so you get the full dose of medicine.
- You will know that the injection has finished when the yellow marker fully appears in the window view and stops moving. See Figure L.

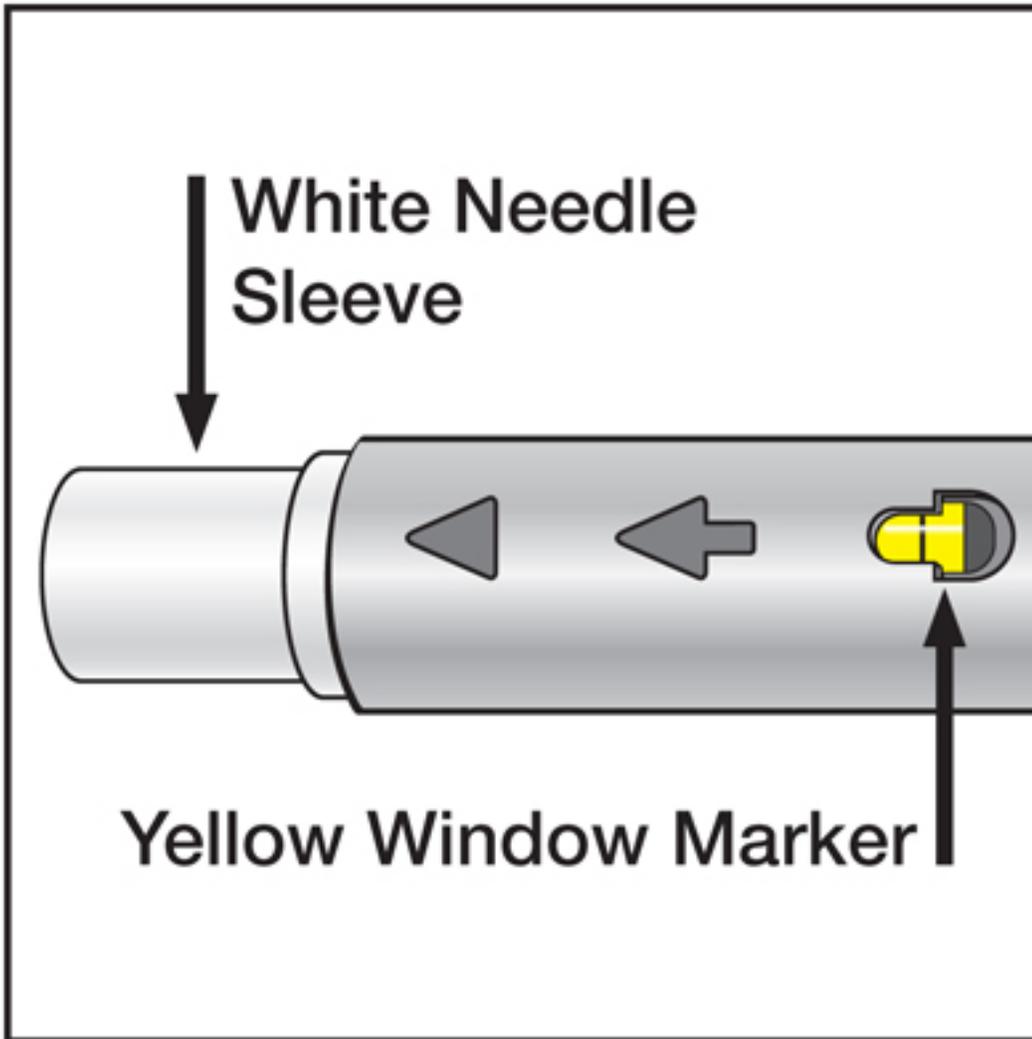
Figure L



19. When the injection is finished, slowly pull the Pen from your skin. The white needle sleeve will move to cover the needle tip. See Figure M.

- Do not touch the needle. The white needle sleeve is there to prevent you from touching the needle.

Figure M



- Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. Do **not** rub the injection site. You may have slight bleeding. This is normal.

20. Dispose of your used HUMIRA Pen. See the section “**How should I dispose of the used HUMIRA Pen?**”

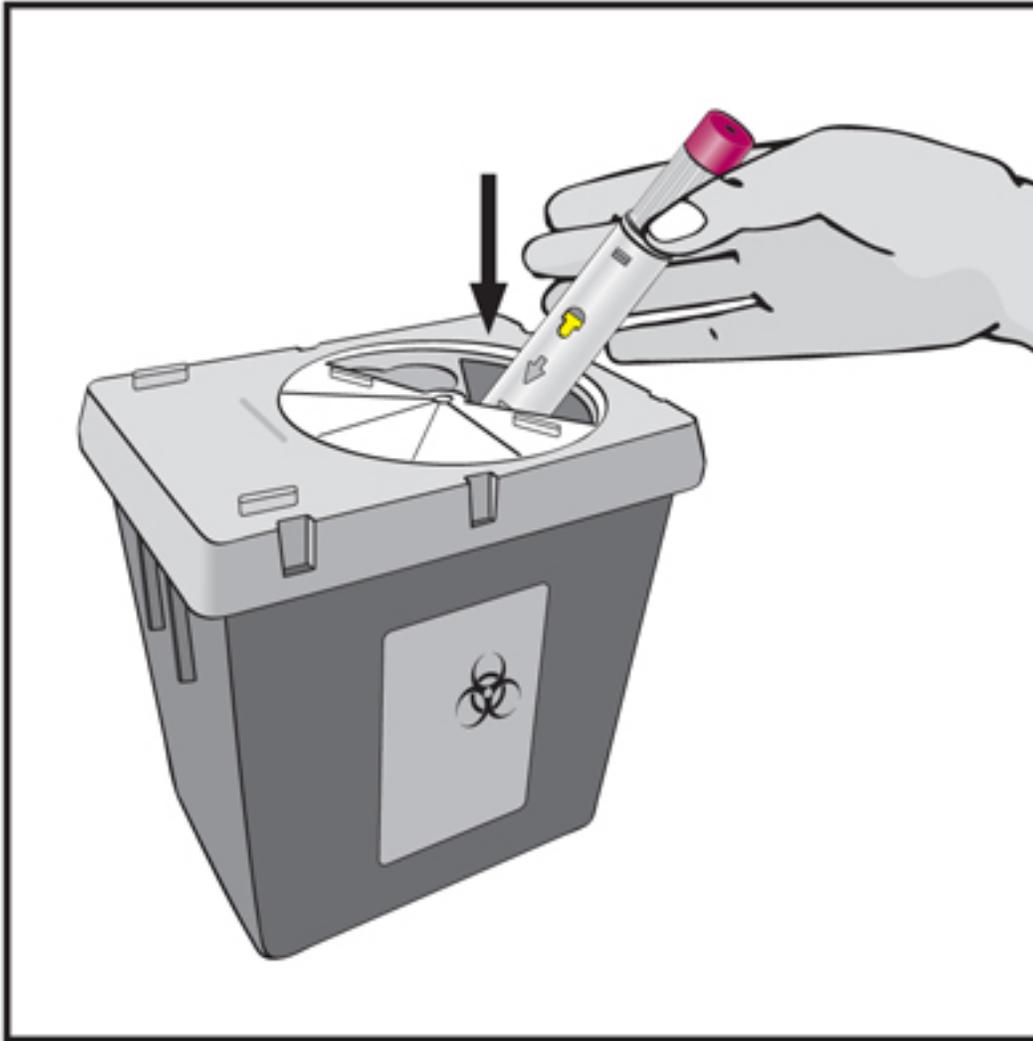
21. Keep a record of the dates and location of your injection sites. To help you remember when to take HUMIRA, you can mark your calendar ahead of time.

How should I dispose of the used HUMIRA Pen?

- Put your Pen in a FDA-cleared sharps disposal container right away after use. See Figure N. **Do not throw away (dispose of) the Pen in your household trash.**

- Do not try to touch the needle. The white needle sleeve is there to prevent you from touching the needle.

Figure N



- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic,
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
 - upright and stable during use,
 - leak-resistant, and
 - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.
- For the safety and health of you and others, never re-use your HUMIRA Pens.
- The used alcohol pads, cotton balls, dose trays and packaging may be placed in your household trash.
- **Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.**
- **Always keep the sharps container out of the reach of children.**

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

AbbVie Inc.

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

Content revised 01/2013

INSTRUCTIONS FOR USE

HUMIRA® (Hu-MARE-ah)

(adalimumab)

SINGLE-USE PREFILLED SYRINGE

Do not try to inject HUMIRA yourself until you have been shown the right way to give the injections. If your doctor decides that you or a caregiver may be able to give your injections of HUMIRA at home, you should receive training on the right way to prepare and inject HUMIRA. It is important that you read, understand, and follow these instructions so that you inject HUMIRA the right way. Call your healthcare provider if you or your caregiver has any questions about the right way to inject HUMIRA.

How should I store HUMIRA?

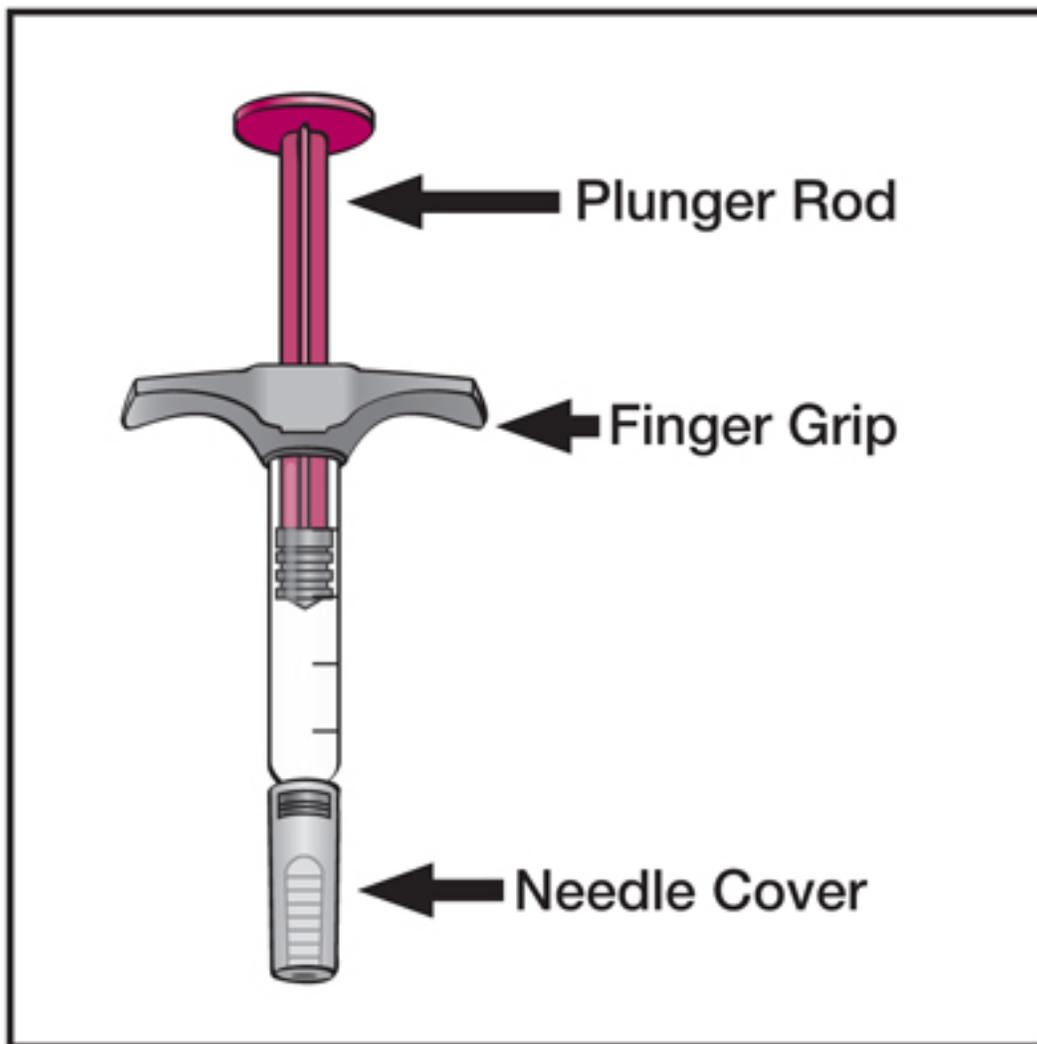
- Store HUMIRA in a refrigerator at 36°F to 46°F (2°C to 8°C) in the original container until it is used. Protect from light.
- When traveling, HUMIRA should be stored in a cool carrier with an ice pack.
- **Do not freeze HUMIRA.** Do not use HUMIRA if frozen, even if it has been thawed.
- Refrigerated HUMIRA may be used until the expiration date printed on the HUMIRA carton, dose tray and prefilled syringe.
- Do not use a prefilled syringe if the liquid is cloudy, discolored, or has flakes or particles in it.
- Do not drop or crush HUMIRA. The prefilled syringe is glass.
- **Keep HUMIRA, injection supplies, and all other medicines out of the reach of children.**

Gather the Supplies for Your Injection

- You will need the following supplies for your injection of HUMIRA.
 - Find a clean, flat surface to place the supplies on.
- 1 alcohol swab
- 1 cotton ball or gauze pad (not included in your HUMIRA carton)
- 1 HUMIRA prefilled syringe (See Figure A)
- 1 FDA-cleared sharps disposal container for HUMIRA prefilled syringe disposal (not included in your HUMIRA carton)

If you do not have all of the supplies you need to give yourself an injection, go to a pharmacy or call your pharmacist. The diagram below shows what a prefilled syringe looks like. See Figure A.

Figure A



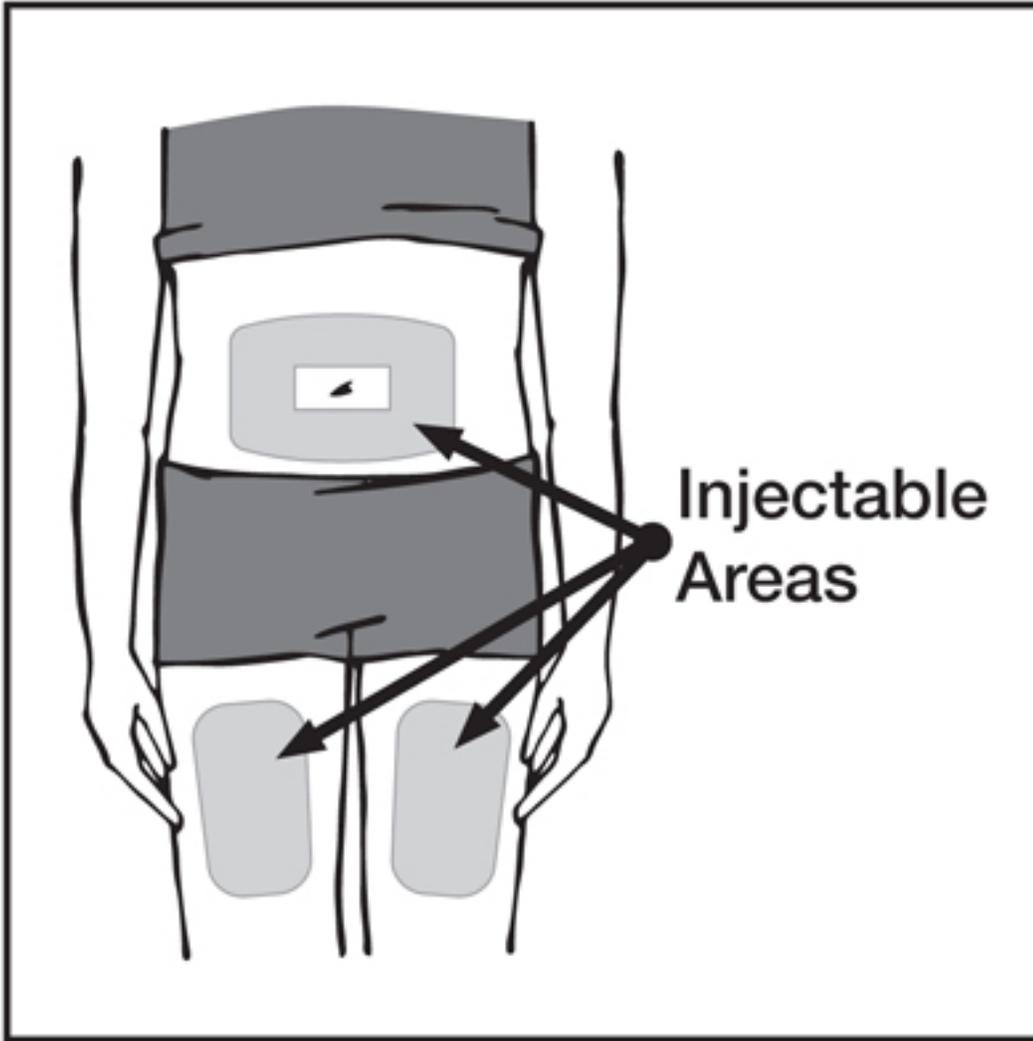
Check the carton, dose tray, and prefilled syringe

1. Make sure the name HUMIRA appears on the dose tray and prefilled syringe label.
2. **Do not use** and call your doctor or pharmacist if:
 - the seals on top and bottom of the carton are broken or missing.
 - the HUMIRA labeling has an expired date. Check the expiration date on your HUMIRA carton and do not use if the date has passed.
 - the prefilled syringe that has been frozen or left in direct sunlight. See the section: **“How should I store HUMIRA?”** at the beginning of these Instructions for Use.
 - the liquid in the prefilled syringe is cloudy, discolored or has flakes or particles in it. Make sure the liquid is clear and colorless.

Choose the Injection Site

3. Wash and dry your hands well.
4. Choose an injection site on:
 - the front of your thighs or
 - your lower abdomen (belly). If you choose your abdomen, do not use the area 2 inches around your belly button (navel). See Figure B.

Figure B



- 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 skin that is:
 - sore (tender)
 - bruised
 - red
 - hard
 - scarred or where you have stretch marks
- If you have psoriasis, do not inject directly into any raised, thick, red or scaly skin patches or lesions on your skin.
- Do not inject through your clothes.

Prepare the Injection Site

5. Wipe the injection site with an alcohol prep (swab) using a circular motion.

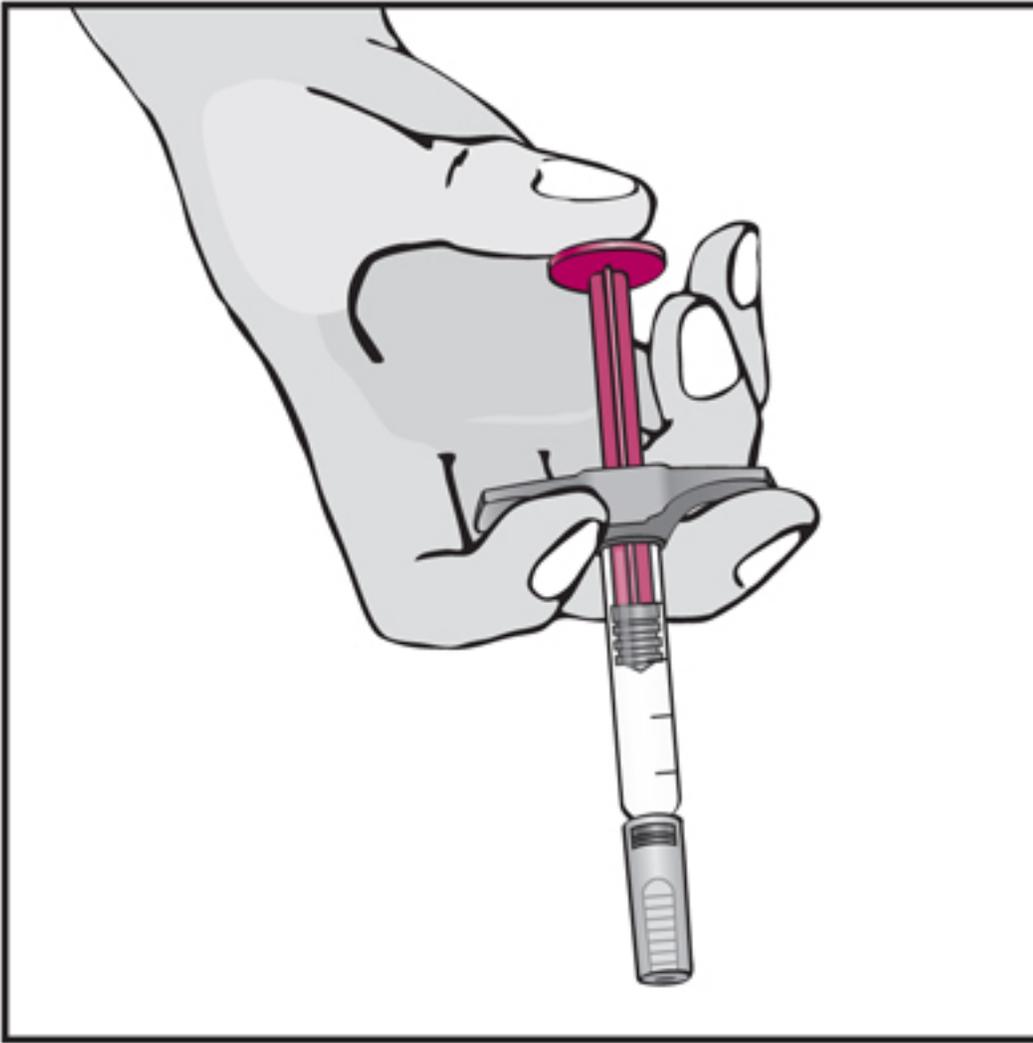
6. Do **not** touch this area again before giving the injection. Allow the skin to dry before injecting. Do not fan or blow on the clean area.

Prepare the Syringe and Needle

7. Check the fluid level in the syringe:

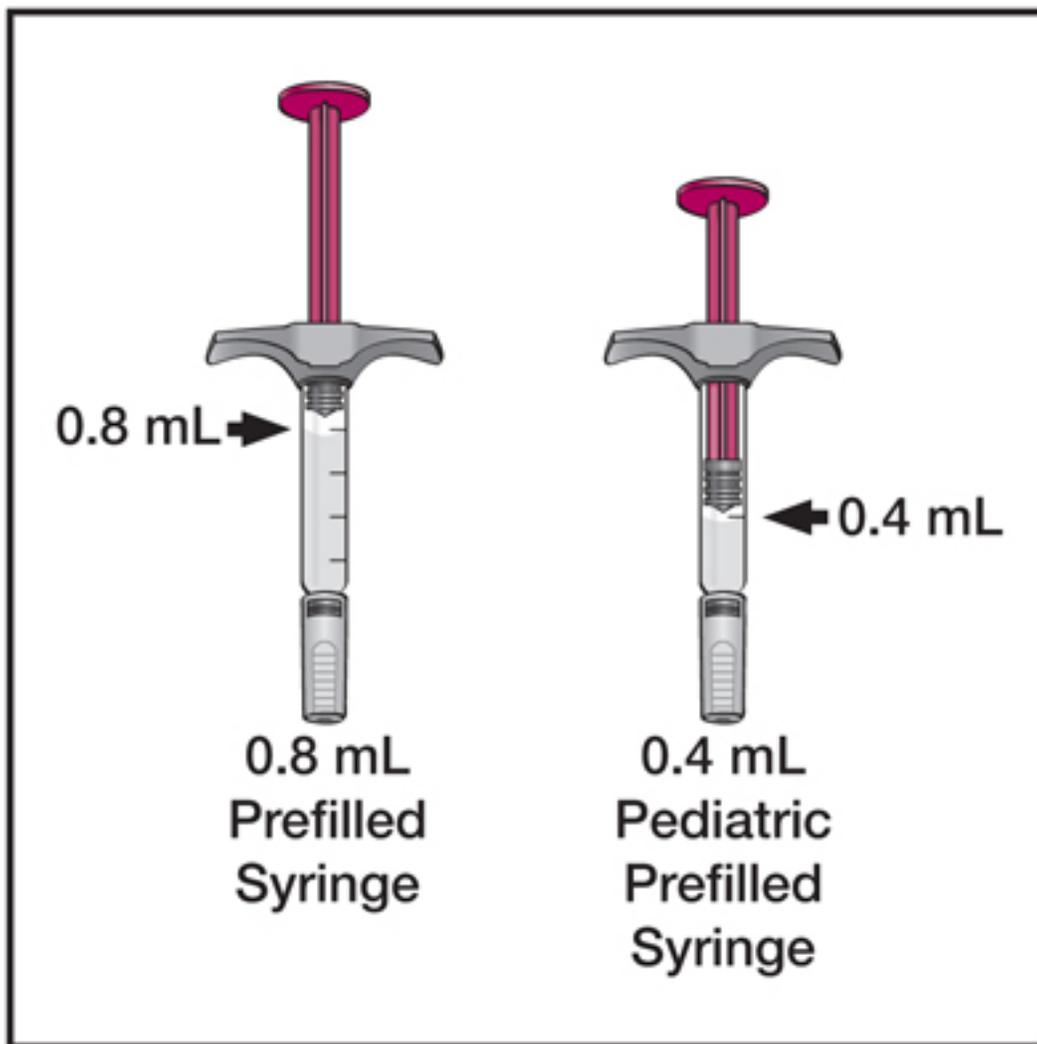
- Always hold the prefilled syringe by the body of the syringe. Hold the syringe with the covered needle pointing down. See Figure C.

Figure C



- Hold the syringe at eye level. Look closely to make sure that the amount of liquid in the syringe is the same or close to the:
- 0.8 mL line for the 40 mg prefilled syringe
- 0.4 mL line for the 20 mg pediatric prefilled syringe. See Figure D.

Figure D



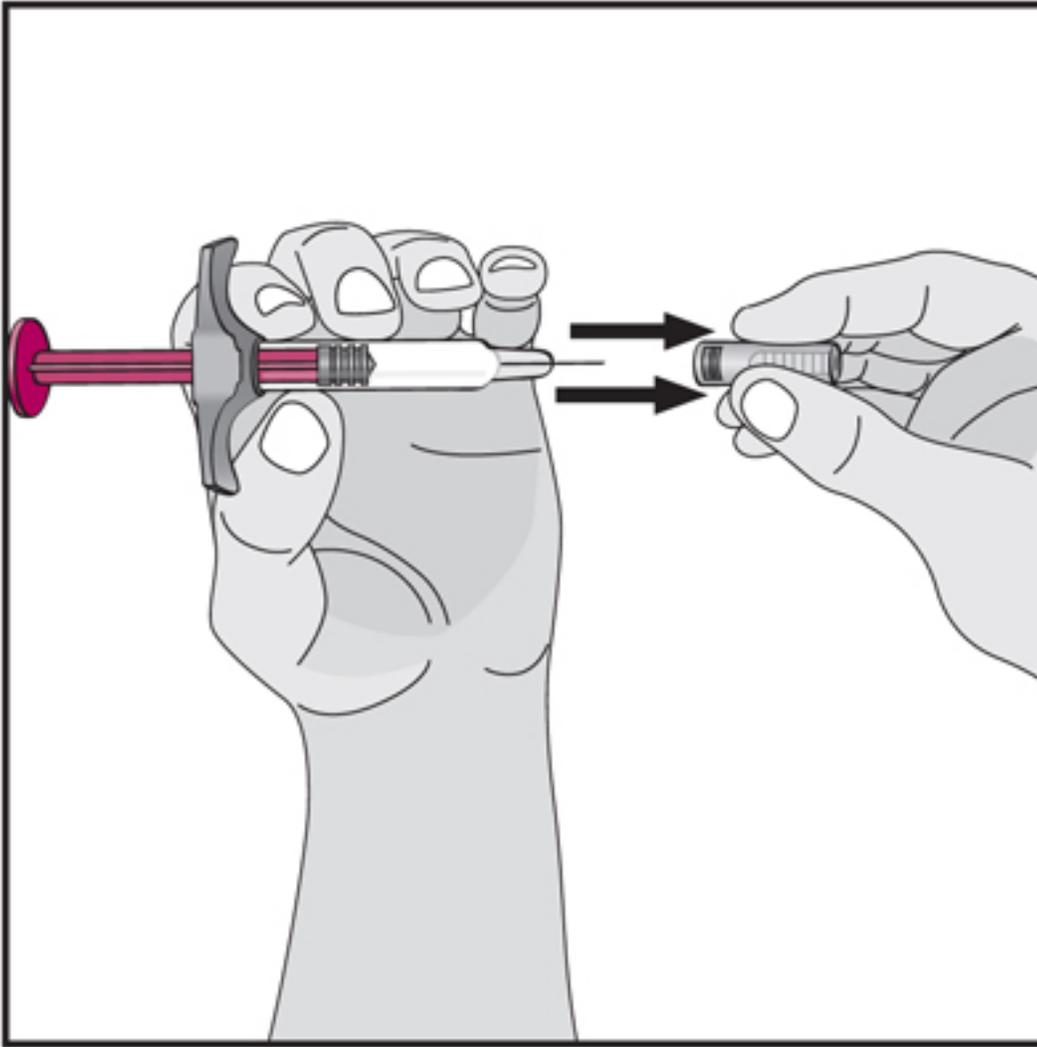
8. The top of the liquid may be curved. If the syringe does not have the correct amount of liquid, **do not use that syringe**. Call your pharmacist.

9. Remove the needle cover:

- Hold the syringe in one hand. With the other hand gently remove the needle cover. See Figure E.

- Throw away the needle cover.

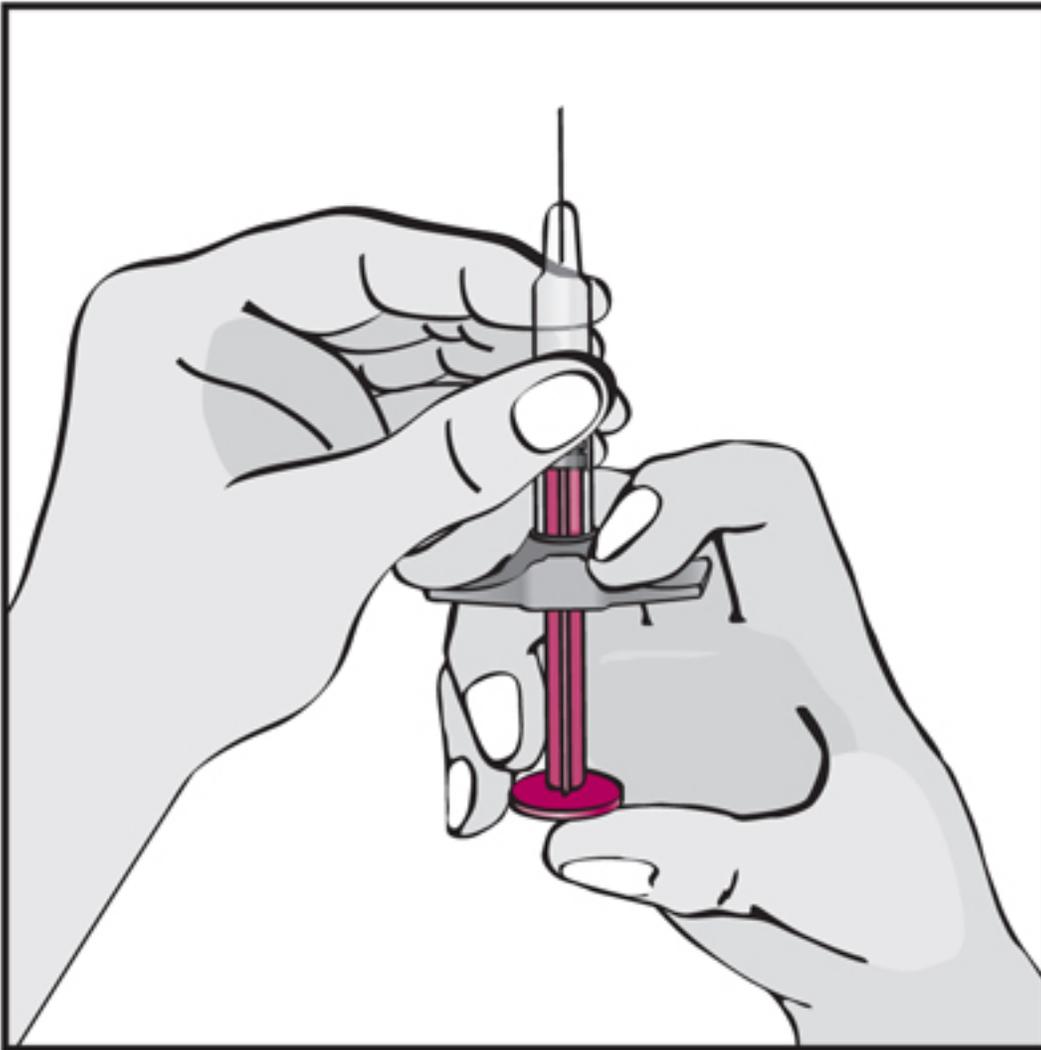
Figure E



- Do not touch the needle with your fingers or let the needle touch anything.

10. Turn the syringe so the needle is facing up and hold the syringe at eye level with one hand so you can see the air in the syringe. Using your other hand, slowly push the plunger in to push the air out through the needle. See Figure F.

Figure F



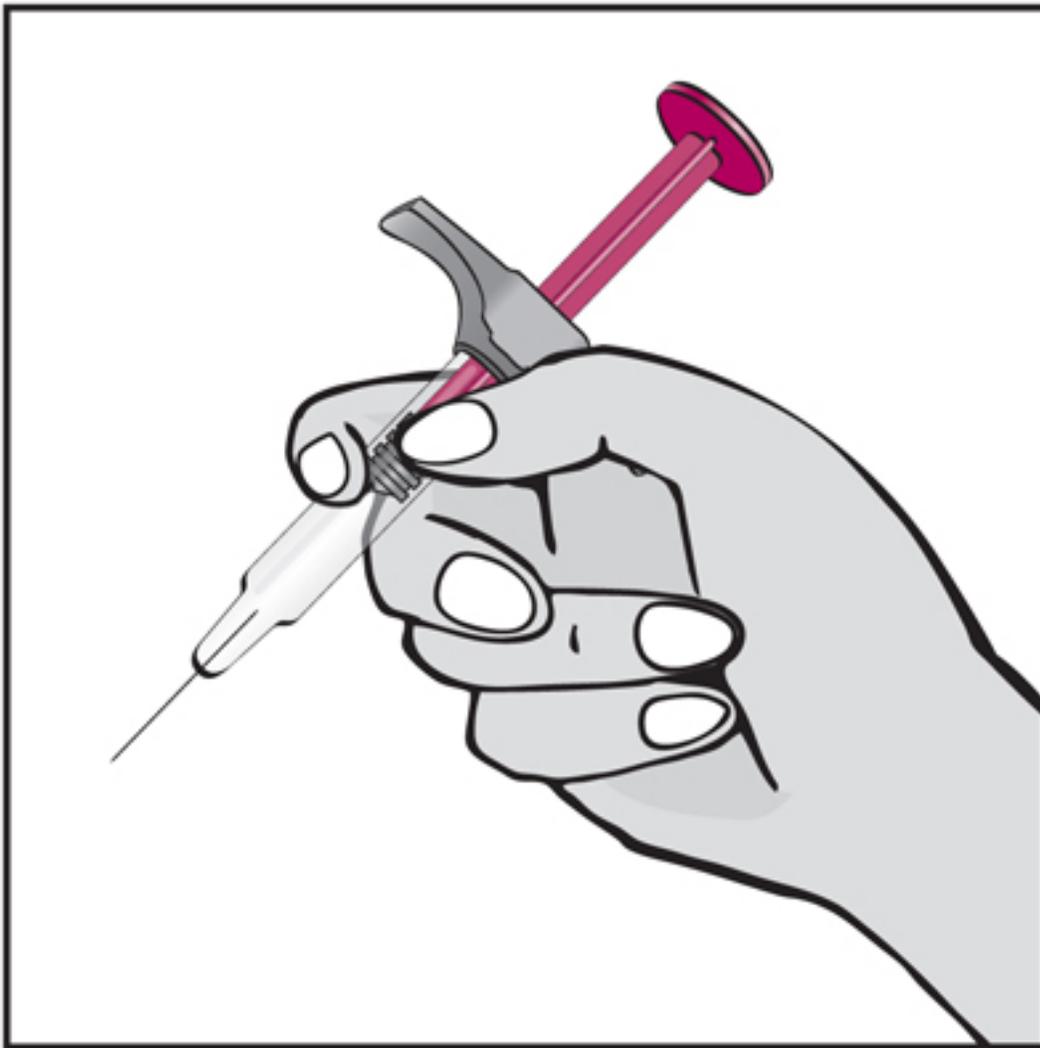
- You may see a drop of liquid at the end of the needle. This is normal.

Position the Prefilled Syringe and Inject HUMIRA

Position the Syringe

11. Hold the body of the prefilled syringe in one hand between the thumb and index finger. Hold the syringe in your hand like a pencil. See Figure G.

Figure G



- **Do not** pull back on the plunger at any time.
- With your other hand, gently squeeze the area of the cleaned skin and hold it firmly. See Figure H.

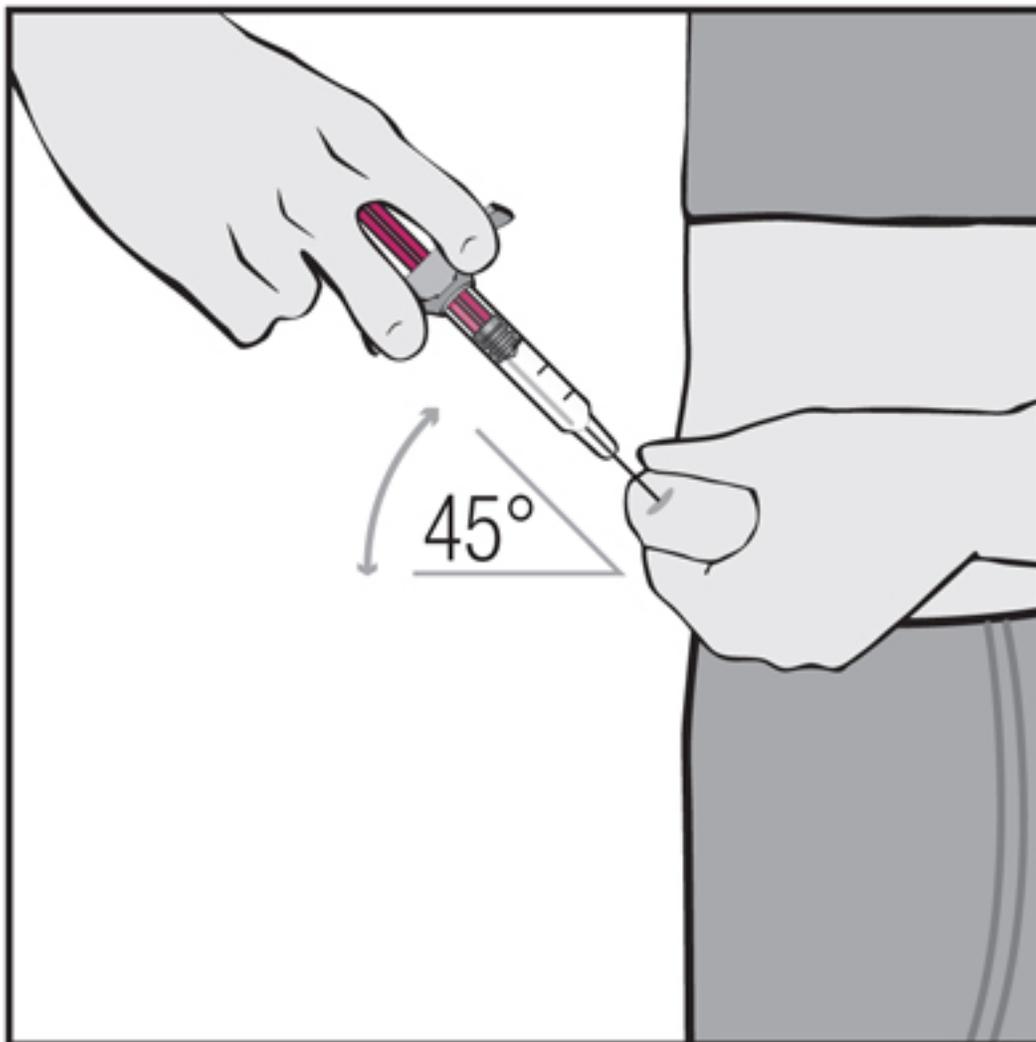
Figure H



Inject HUMIRA

12. Using a quick, dart-like motion, insert the needle into the squeezed skin at about a **45-degree angle**. See Figure I.

Figure I

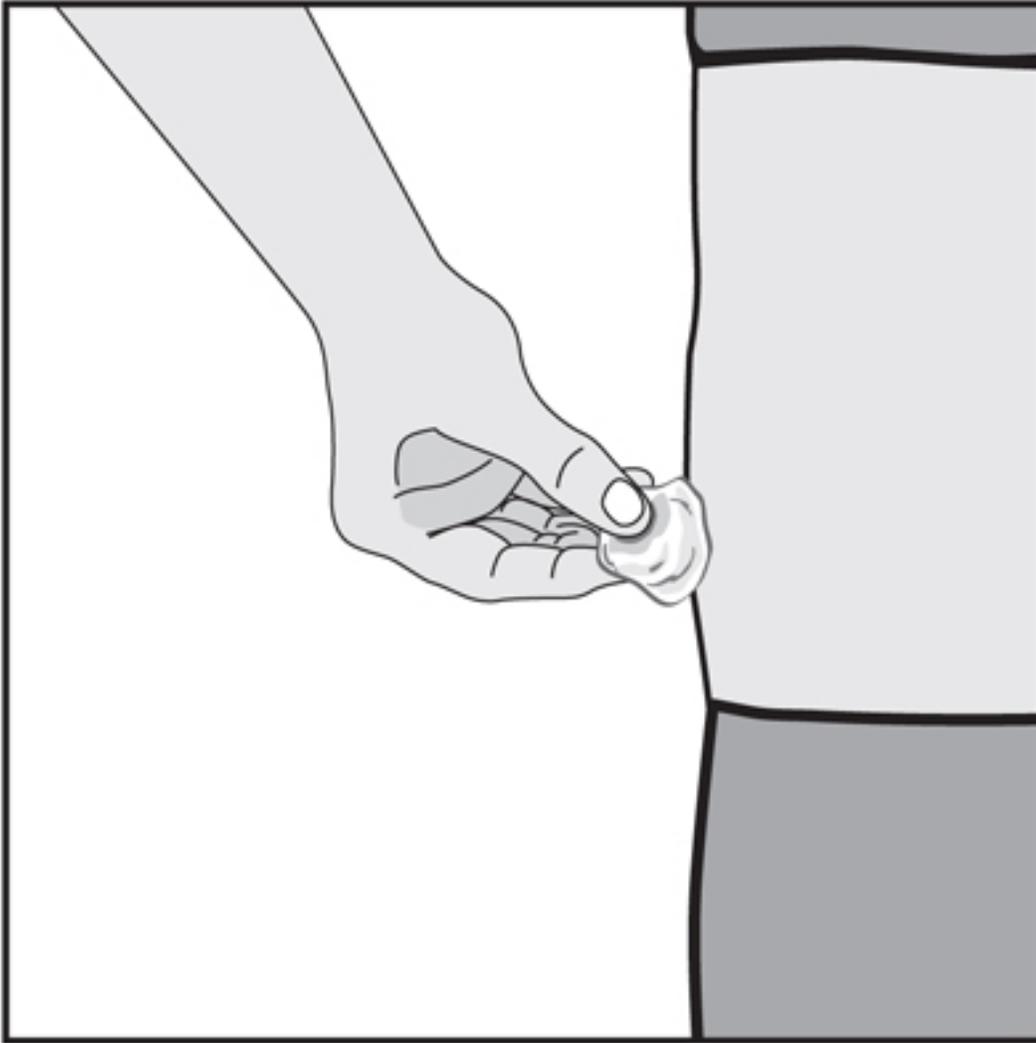


- After the needle is in, let go of the skin. Pull back gently on the plunger.

If blood appears in the syringe:

- It means that you have entered a blood vessel.
- **Do not inject HUMIRA.**
- Pull the needle out of the skin while keeping the syringe at the same angle.
- Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. See Figure J.

Figure J



- **Do not** use the same syringe and needle again. Throw away the needle and syringe in your special sharps container.
- **Do not** rub the injection site. You may have slight bleeding. This is normal.
- Repeat Steps 1 through 12 with a new prefilled syringe.

If no blood appears in the syringe:

- Slowly push the plunger all the way in until all of the liquid is injected and the syringe is empty.
- Pull the needle out of the skin while keeping the syringe at the same angle.
- Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. **Do not** rub the injection site. You may have slight bleeding. This is normal.

13. Throw away the used prefilled syringe and needle. See **“How should I dispose of used prefilled syringes and needles?”**

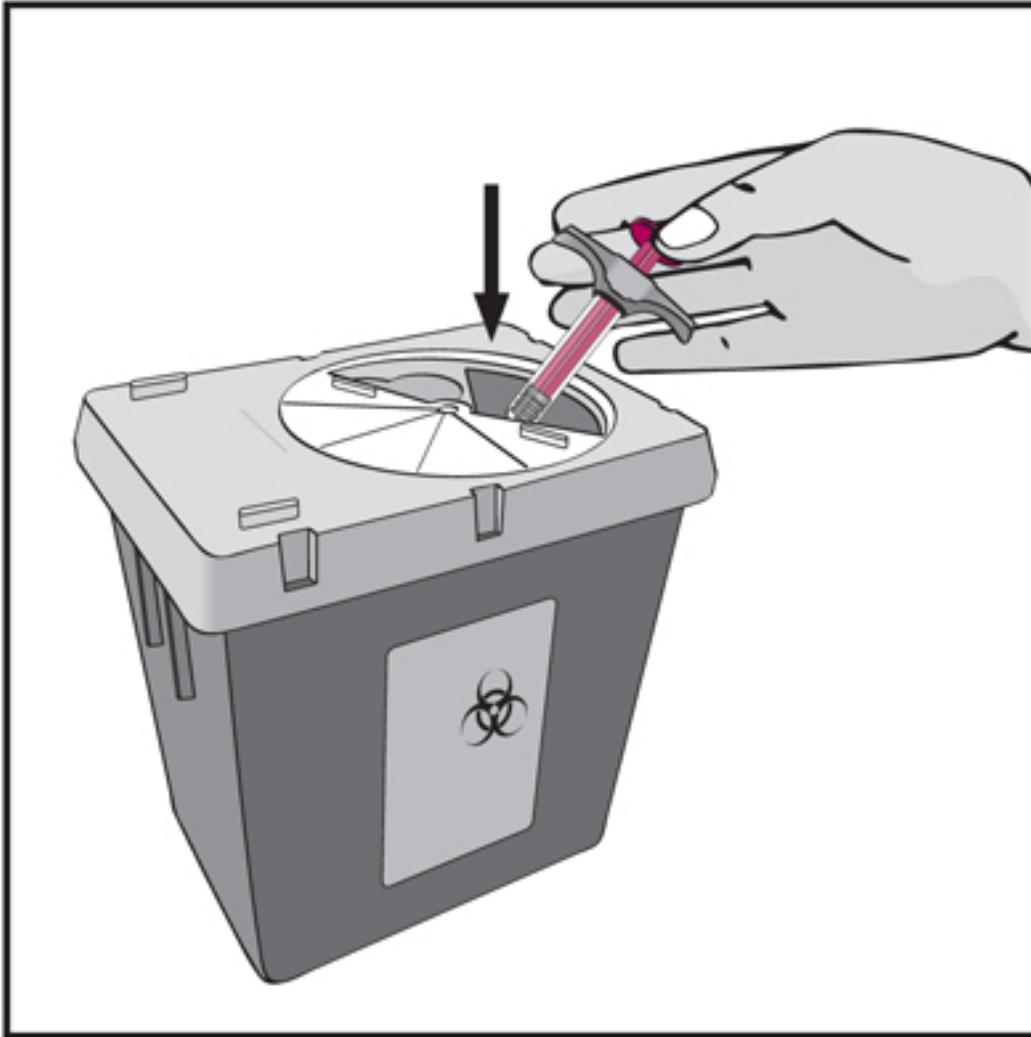
14. Keep a record of the dates and location of your injection sites. To help you remember when to take HUMIRA, you can mark your calendar ahead of time.

How should I dispose of used prefilled syringes and needles?

- **Put your used needles and syringes in a FDA-cleared sharps disposal container right away after use.** See Figure K. **Do not throw away (dispose of) loose needles and syringes in your household trash.**

- Do not try to touch the needle.

Figure K



- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic,
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
 - upright and stable during use,
 - leak-resistant, and
 - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.
- For the safety and health of you and others, needles and used syringes **must never** be re-used.
- The used alcohol pads, cotton balls, dose trays and packaging may be placed in your household trash.
- **Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.**
- **Always keep the sharps container out of the reach of children.**

This Instructions for Use has been approved by the U.S. Food and Drug Administration.
AbbVie Inc.
North Chicago, IL 60064, U.S.A.
Content revised 01/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125057Orig1s322

CROSS DISCIPLINE TEAM LEADER REVIEW



Memorandum

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Pulmonary, Allergy, and
Rheumatology Products, HFD-570
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: April 17, 2013
From: Sarah Yim, M.D.
Associate Director, Rheumatology
To: BLA 125057 supplement 322
Subject: Humira institutional use 40 mg/0.8 mL vial

This supplement biologic license application is for the re-introduction of a 40 mg/0.8 mL vial presentation of adalimumab (Humira®) for institutional use. As per the Product Quality review by Dr. Jun Park, the original approval of adalimumab in 2002 included a 40 mg/0.8 mL vial presentation for both patient and institutional use. The sponsor ceased marketing this presentation and removed information about it from the United States Prescribing Information (USPI) in 2004. Currently, adalimumab is available as a 40 mg/0.8 mL autoinjector (Humira pen), a 40 mg/0.8 mL pre-filled syringe (PFS), and a 20 mg/0.4 mL PFS; all for single-use. With this submission, the sponsor seeks to re-introduce the 40 mg/0.8 mL vial presentation for institutional use only. In order to do this, the vial drug product manufacturing site had to be changed from the original BLA. The sponsor proposes to manufacture the 40 mg/0.8 mL vial presentation at the same facility that manufactures the 20 mg/0.4 mL PFS (b) (4)

The Product Quality review team from the Office of Biotechnology Products, Division of Monoclonal Antibodies, has reviewed the information submitted on the manufacturing process, transfer, and validation for the vials manufactured at (b) (4). Based on batch analysis and stability data, the adalimumab 40 mg/0.8 mL vials manufactured at (b) (4) are comparable with adalimumab PFS manufactured at the approved adalimumab drug product facilities. The (b) (4) site was inspected on July 9-17, 2012 and classified No Action Indicated. The Product Quality team recommends approval of this supplement.

The carton and container labels for the institutional use vial were reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) reviewer, Teresa McMillan, Pharm.D., and OBP labeling reviewer Kimberly Rains, Pharm.D. Minor revisions were recommended from the proposed labeling and were accepted by the sponsor.

Prescribing information changes are limited to those needed to accommodate the vial

configuration and are as follows:

- Highlights, Dosage Forms and Strengths: “Injection: 40 mg/0.8 mL in a single-use glass vial for institutional use only.”
- Section 2.7 General Considerations for Administration: “The Humira institutional use vial is for use and administration within an institutional setting only, such as a hospital, physician’s office or clinic. Withdraw the dose using a sterile needle and syringe and administer promptly by a healthcare provider within an institutional setting. Only administer one dose per vial. The vial does not contain preservatives; therefore discard unused portions.”
- Section 3 Dosage Forms and Strengths: “Institutional Use Vial -- Injection: a single-use, glass vial, providing 40 mg (0.8 mL) of Humira for institutional use only.”
- Section 16 How Supplied/Storage and Handling: (b) (4) is struck out, leaving the phrase, “Humira (adalimumab) is supplied as a preservative-free, sterile solution for subcutaneous administration. The following packaging configurations are available.” Also added is “Institutional Use Vial Carton – 40 mg. Humira is supplied for institutional use only in a carton containing a single-use glass vial, providing 40 mg (0.8 mL) of Humira. The NDC number is 0074-3797-01.”

These proposed changes are acceptable. No further changes to the prescribing information were proposed.

Conclusion: sBLA 125057 supplement 322 for the reintroduction of an institutional use vial configuration is acceptable for approval.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SARAH K YIM
04/17/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125057Orig1s322

CHEMISTRY REVIEW(S)



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Division of Monoclonal Antibodies
Rockville, MD 20852
Tel. 301-827-0850

Memorandum of Review

Date: April 10, 2013
To: File for STN: 125057/322
RPM: Sadaf Nabavian, CDER/ODEII/DPARP
From: Jun Park, Product Reviewer, DMA/OBP/CDER, HFD-123
Through: Laurie Graham, Team Leader, DMA/OBP/CDER
Patrick Swann, Deputy Division Director, DMA/OBP/CDER
Applicant: AbbVie Inc
Product: Humira® (adalimumab)
Supplement Receipt Date: November 16, 2012
Action Due Date: May 18, 2013
Review Recommendation: Approval from a CMC perspective.

SUMMARY: The original approval of adalimumab in 2002 included a 40 mg/0.8 mL vial presentation for both patient and institutional use. However, the vial presentation is not marketed in the US and was removed from the prescribing information in 2004. The current US prescribing information for adalimumab only includes pre-filled syringes (40 mg/0.8 mL and 20 mg/0.4 mL) and pens (40 mg/0.8 mL). This sBLA is to reintroduce an adalimumab 40 mg/0.8 mL vial presentation to the How Supplied section of the Humira prescribing information. The vial presentation, however, will be for institutional use only. The intent is to make Humira available in institutional setting for appropriate candidates.

In order to re-introduce the vial presentation in the US, the vial DP manufacturing site had to be changed from the one approved in the original BLA. The sponsor proposes to manufacture the 40 mg/0.8 mL vial presentation at the same site that manufactures the 20 mg/0.4 mL pre-filled syringes (PFS). Specifically, this submission updates the vial DP manufacturing sites from

(b) (4)

The process for manufacturing of adalimumab 40 mg/0.8 mL vials has been transferred and validated at the

(b) (4)

The validation lots met all in-process testing and release specifications and have been placed on stability.

The sponsor submitted responses to an information requests (IR) dated 3/15/2013. I reviewed these responses and found that they are acceptable.

Based on the studies for the batch analysis and stability data, the adalimumab 40 mg/0.8 mL vials manufactured at the [REDACTED] (b) (4) [REDACTED] are comparable with the adalimumab in prefilled syringes (PFS) manufactured at the approved adalimumab drug product facilities.

I found that the PAS is approvable from a CMC perspective.

It is noted that the sponsor provided updated carton and container labeling, as well as prescribing information. The carton and container labeling is deferred to DMEPA and Kimberly Rains of OBP.

For the prescribing information, the sponsor updated: the dosage forms and strengths section of the highlights, section 2.7 General considerations for Administration, section 3 Dosage forms and Strengths, and section 16 How Supplied/Storage and Handling. The review of the prescribing information is deferred to DMEPA, Kimberly Raines of OBP, and DPARP.

Conclusions:

- I. Recommendation: Approval from CMC perspective.
- II. Sections deferred to other reviewers: Review of the carton and container and prescribing information was deferred to DPARP, DMEPA and Kimberly Rains of OBP
- III. Post-marketing commitments: None
- IV. Future Inspection Items: The over-fill data with the vial adapters used to justify the increased fill volume for the vials.

cc:

Park/Laurie Graham
DMA Drive
DMA Paper Files

HFD-123
BLA (STN: 125057/322)
BLA (STN: 125057/322)

REVIEW

The Sponsor's Responses to the March 15, 2013 Information Requests (IR):

1. Provide a justification for the increase in the fill volume for the drug product (DP) in the vial presentation from (b) (4) mL to (b) (4) mL, particularly as the new fill volume would appear to exceed the excess volume recommendations from (b) (4). In addition, provide a justification for the use of only one validation run with the new fill volume.

Sponsor's Response: The sponsor indicates that they anticipate that institutional health care professionals may use vial adaptors in the removal of Humira from the vials. The sponsor indicates that vial studies were conducted that revealed that an even higher excess fill volume (target (b) (4) mL) was required to assure a 0.8 mL drug delivery from the vial when aspirated and dispensed using a vial adapter, syringe and injection needle. Therefore, to account for the potential use of vial adaptors, a higher volume is recommended to assure a full dose is available for use in that setting.

While there was only 1 validation batch using the (b) (4) mL target fill volume, there are now 7 post-validation lots. **Post-validation monitoring** has shown that the higher targeted (b) (4) mL fill volume has been consistently and accurately met by the filling process (Table 1).

Table 1. Fill Volume Summary for Vial Lots – Process Validation and Overall

Fill Volume (mL)	PV1	PV2	PV3	PV4	Post-Val
	83433SP	83443SP	84457SP	91070SP	n=7
Target	(b) (4)				
Mean					
StDev.					

Reviewer's Comment: I found that these are acceptable.

Comment by L. Graham: The sponsor did not provide any data, using vial adaptors, to justify the increased fill volume of the vials. With the proposed process, there would be a (b) (4) mL over-fill of the vials. I reviewed information from several other BLAs that use vials and found that the over-fill suggested by the sponsor to be reasonable. The data to support the fill volume can be reviewed on the next inspection.

2. Provide summary information to support the comparability of the vial DP with the pre-filled syringe (PFS). This comparability assessment should include the use of acceptance criteria based on historical release as well as real time, accelerated, and stressed stability data.

Sponsor's Response: The sponsor provided a table comparing historical mean + SD release results of 105 PFS batches to 6 vial presentation DP batches. A detailed comparison for the manufacturing process and in-process controls at (b) (4) for Humira PFS and Vial was also provided. The sponsor stressed the (b) (4) is the DP manufacturer for both vials and pre-filled syringes and the DP manufacturing process, and in-process controls are the same with the exception of the (b) (4) used for filling.

Reviewer's Comment: *There are no process changes between the (b) (4). The data provided are acceptable. See also the 3.2.P.5.4 section in this report.*

Comment by L. Graham: *The release results comparison provided by the sponsor, as well as the comparison performed by Jun in his review below (section 3.2.S.P.5.4), support comparability.*

The sponsor also provided a comparison of real time, accelerated and stressed stability data for vial drug product batches and the approved Humira PFS batches. This included a summary of the results obtained for the stability-indicating size exclusion HPLC (SE-HPLC), in vitro TNF neutralization and cation exchange HPLC (CEX HPLC) assays. The comparison for the vial batches is presented in Table 4 through Table 9.

Table 4. Comparison of SE-HPLC Stability Data for Vials Registration and Process Validation Lots With Approved Humira PFS Lots

Test	Shelf Life Specification	Lot Interval (month)	Vial Lots			PFS Lots		
			+5°C	+25°C/ 60%RH	+40°C/ 75%RH	+5°C	+25°C/ 60% RH	+40°C/ 75%RH
SE-HPLC	(b) (4) principal peak (monomer)	Initial	(b) (4)	-	-	(b) (4)	-	-
		3	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	
		6	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	
		9	(b) (4)	-	-	(b) (4)	-	-
		12	(b) (4)	-	-	(b) (4)	-	-
		18	(b) (4)	-	-	(b) (4)	-	-
		24	(b) (4)	-	-	(b) (4)	-	-

Table 5. Comparison of In Vitro TNF Neutralization Stability Data for Vials Registration and Process Validation Lots With Approved Humira PFS Lots

Test	Shelf Life Specification	Lot Interval (month)	Vials			PFS		
			+5°C	+25°C/ 60%RH	+40°C/ 75%RH	+5°C	+25°C/ 60%RH	+40°C/ 75%RH
In vitro TNF Neutralization	(b) (4) of the neutralization capacity of the reference standard	Initial	(b) (4)	-	-	(b) (4)	-	-
		3	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	
		6	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	
		9	(b) (4)	-	-	(b) (4)	-	-
		12	(b) (4)	-	-	(b) (4)	-	-
		18	(b) (4)	-	-	(b) (4)	-	-
		24	(b) (4)	-	-	(b) (4)	-	-

* Inverted vial stability data used for this batch

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Reviewer’s Comment: *The sponsor compared stability data between the vial drug product batches and the approved Humira PFS batches under real time, accelerated and stressed conditions. Although the sponsor didn’t conduct a statistical analysis, I found that the stability data between the vial drug product batches and the approved Humira PFS batches at the real time, accelerated and stressed conditions are comparable.*

These are acceptable

Comment by L. Graham: *The sponsor did not provide a statistical comparison of the trend lines for the stability data. However, I concur with Jun that the stability data provided comparing the vials to mean +/- SD results for the PFS lots, as well as the data provided in 3.2.P.8 of the submission, support comparability.*

3. Provide clarification on any difference in drug product specifications between the vial and PFS DP. For example, it is noted that many of the CEX-HPLC release acceptance criteria for the PFS are listed as “not tested” for the vial DP.

Sponsor’s Response: The sponsor indicated that specifications submitted for the vial (b) (4) are the same as the currently approved specifications for the 40 mg/0.8 mL and 20 mg/0.4 mL PFS, except the measurement of forces test which is not applicable to the vial. The specifications for both presentations are listed in Table 10.

Table 10. Specifications for Humira PFS and Vial

Test	PFS Acceptance Criteria	Vial Acceptance Criteria
Appearance		
Description	Pre-filled syringes with aqueous solution	Glass Vials with aqueous solution The vial closure looks intact
Clarity	Not more opalescent than reference suspension (b) (4)	Not more opalescent than reference suspension (b) (4)
Color	Not more intensely colored than reference solution (b) (4)	Not more intensely colored than reference solution (b) (4)
Identity		
Cation Exchange HPLC	The peak pattern complies with that of the characterized reference standard	The peak pattern complies with that of the characterized reference standard
Purity		
Cation Exchange HPLC	(b) (4)	

Table 10. Specifications for Humira PFS and Vial (Continued)

Test	PFS Acceptance Criteria	Vial Acceptance Criteria
Purity (continued)		
Size Exclusion HPLC	Release	Release
	(b) (4)	(b) (4)
Sterility: Filled Drug Product	No growth appears in the test	No growth appears in the test
		(b) (4)
Potency		
In vitro TNF Neutralization	(b) (4)	
Quantity		
Protein Content (UV 280 nm)	(b) (4)	
General Tests		
pH	(b) (4)	
Osmolarity	(b) (4)	
Pharmaceutical Tests		
Particulate Matter Visible Particles	(b) (4)	
Particulate Matter Subvisible Particles	The solution must meet the requirements for small volume injections	The solution must meet the requirements for small volume injections
		(b) (4)
Volume in Container	The volume measured for each container is not less than the labeled volume Test 5 containers	The volume measured for each container is not less than the labeled volume Test 5 containers
Container Closure Integrity	Release	Release
	Not Tested	Not Tested
		(b) (4)
	Test 20 Containers	Test 20 Containers
Measurement of Forces	Release	N/A
	Not Tested	
	(b) (4)	

Reviewer’s Comment: *These are acceptable.*

Comment by L. Graham: *The specifications listed in the BLA for the PFS are not the same as provided by the sponsor in the table above. It appears that, in the past, the sponsor updated the official specification for the PFS in the BLA with the filing of (b) (4). However, this PAS received a (b) (4). The sponsor (b) (4). In addition, with the filing of (b) (4), the sponsor updated the specifications for DP to include a (b) (4) presentation. However, this (b) (4) received a (b) (4). The sponsor (b) (4) specifications from the BLA.*

A comment will be sent to the sponsor that they need to update the BLA with the correct specifications. The sponsor provided the updated specifications on 3/28/2013, as an amendment to the current PAS.

Overview of Manufacturing Changes

With the original approval of the BLA, Abbott had registered (b) (4) (b) (4), as the DP manufacturer for the 40 mg/0.8 mL vial presentation. This supplement supports the transfer of the vial DP manufacturing location from (b) (4) (b) (4) to the site that manufactures the 40 mg/0.8 mL PFS (b) (4) (b) (4).

- The manufacturing process for the bulk drug product solution used to fill the vials has been updated to align with the manufacturing process approved for the bulk pre-filled syringe (PFS) dosage/presentation
- The manufacturing process for bulk adalimumab 50 mg/mL solution for injection, 40 mg/0.8 mL vials is identical to the manufacturing process for bulk adalimumab 50 mg/mL solution for injection, 40 mg/0.8 mL pre-filled syringes with the exception of the a different container closure system.
- The same equipment is used at (b) (4) for processing a (b) (4) batch size range of adalimumab bulk drug product solution for pre-filled syringe manufacturing
- New (b) (4) stopper vial closures and (b) (4) caps with (b) (4) will also be used to manufacture the bulk vials. The original (b) (4) stopper has been changed from a (b) (4) stopper, (b) (4) stopper, also (b) (4)
- For future application, the nominal fill volume for the bulk vial has also been increased from the original (b) (4) mL/vial nominal target to a nominal target fill volume of (b) (4) mL/vial to assure delivery of the full dose. **The approved normal fill volume for the adalimumab in PFS presentation is (b) (4) mL.**
- The (b) (4) site was approved to supply the vial presentation to the European Union in March 2011
- The process for manufacturing of adalimumab 40 mg/0.8 mL vials has been transferred and validated at the (b) (4) (b) (4)

3.2.P.1. Adalimumab 40 mg solution for injection 0,8 ml vial Composition

The composition of the 50 mg/mL adalimumab bulk drug product solution used in the manufacture of the 40 mg/0.8 mL pre-filled vial is identical to that used for production of the approved 40 mg/0.8 mL pre-filled syringe and has not been changed from the composition submitted in the original BLA.

3.2.P.2. Manufacturing Process Development

Reviewer's note: refer to the overview of the manufacturing changes and process validation summary in the report.

3.2.P.3 Manufacture of Adalimumab Solution for Injection, 50 mg/mL

3.2.P.3.1 Manufacturers

(b) (4)

3.2.P.2.3 Batch Formula for Adalimumab 50 mg/mL Solution for Injection, 40 mg/0.8 mL Vial

Note: same as those for the PFS presentation

3.2.P.3.3 Manufacturing Process

The manufacturing process for bulk adalimumab 50 mg/mL solution for injection, 40 mg/0.8 mL vials is identical to the manufacturing process for bulk adalimumab 50 mg/mL solution for injection, 40 mg/0.8 mL pre-filled syringes with the exception of the container closure system.. The same equipment is used at (b) (4) for processing a (b) (4) batch size range of adalimumab bulk drug product solution for pre-filled syringe manufacturing.

The manufacturing process for adalimumab 50 mg/mL solution for injection, 40 mg/0.8 mL vial at (b) (4) (b) (4)

(b) (4)

The manufacturing instructions document (b) (4) includes a description of the bulk vial manufacturing process and in-process controls.

Note: a diagram of the manufacturing process is listed below, which is obtained from the submission.

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

3.2.P.3.5 Process Validation

Manufacturing process validation was performed at (b) (4) at nominal batch sizes of approximately (b) (4) of adalimumab bulk drug product solution, per the validation protocols (b) (4) and (b) (4).

Vials for **three drug product batches (83433SP, 83443SP and 84457SP)** filled to a nominal target of (b) (4) mL/vial were produced and tested as described in validation protocol (b) (4).

To assure delivery of the full dose (0.8 mL adalimumab solution for injection) from the vial, adalimumab vials for one additional drug product batch (91070SP) filled to a nominal target of (b) (4) mL/vial was produced according to process validation protocol (b) (4).

The results of all four of the manufacturing process validation runs are provided in Validation Report (b) (4). The remaining information on the validation is from this validation report.

The validation included results for normal in-process control, additional in-process testing for specific steps, and release results. The validation information summarized below is from validation report (b) (4).

Below is a batch genealogy summary for the 4 process validation batches.

Table 1: Product and Process Identification for Process Validation Runs

	Vial Validation lots			
Product name	HUMIRA (adalimumab) 40 mg / 0.8 mL vial			
Lot No.	83433SP	83443SP	84457SP	91070SP
				(b) (4)
Used Drug Substance	50049 BF	50049 BF	59027 BF	59027 BF
Batch No.	50049 BF	50050 BF	59027 BF	50049 BF
Batch size				(b) (4)
	(b) (4)			

Reviewer's Comment: the approved PFS process can cover (b) (4) range, which was validated previously for this DP facility. I believe this is acceptable.

3.5.1.1 (b) (4) active ingredient

The (b) (4) adalimumab DS was shipped to (b) (4) in (b) (4). The DS is (b) (4) at (b) (4). The DS is contained within several (b) (4)

The normal IPC for this step are (b) (4). The IPC information for the DS lots used in the 4 validation runs is shown in the table below, taken directly from the submission.

(b) (4)

4 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page



Reviewer's Comments: *The sponsor noted in the submission that minor and major defects were found with Lot 91070SP (Lot 4 in Table 14 above). These defects were caused by the following deviations:*

- *Deviation (b) (4): the wrong (b) (4) was used for the filling step. Vials that were impacted by this deviation were excluded.*
- *Deviation (b) (4): For Lot 91070SP, in the (b) (4) of this lot (b) (4) vials (3.42%) were sorted out due to the observed da (b) (4) de of the vials in the area of the vial neck. The sponsor claims that the most probable cause for the deviation was that the observed defects were generated at the (b) (4). The damaged vials were effectively removed during the (b) (4). I don't think that the deviations impact the process validation..*

3.5.1.9 Final release (Abbott)

The vials were tested according to current specifications for adalimumab 40 mg, solution for injection 0.8 mL, vials. **All validation lots met all in-process testing and release specifications.**

3.5.1.10 Storage and holding conditions

All storage and holding conditions for the process validation lots complied with the batch record and/or validation protocol requirements. The results are summarized in Table 15.

Table 15 Storage and Holding Conditions

Step	Time	Temperature	Lot 1	Lot 2	Lot 3	Lot 4
(b) (4)						

Reviewer’s Comments:

The validation lots met all in-process testing and release specifications and have been placed on stability. I found that these are acceptable.

A compliance reviewer (BMAB) will review all storage and holding conditions for the process validation lots with regard to microbial control

(b) (4)

Reviewer's Comments: I found that the release specifications for adalimumab vials are identical to those for adalimumab PFS presentations.

3.2.P.5.4 Analytical Procedure

Reviewer's Comments: The sponsor noted that test methods considered equivalent use identical analytical procedures to those identified in the specification. The methods are modified to fulfill local requirements (e.g. document numbering/naming conventions, worksheet format).

I also found that a container closure integrity test is used for stability testing of adalimumab 40 mg/0.8 mL vials, while sterility testing is used for the PFS.

Container Closure Integrity (RTM.P-008304A)

The container closure integrity of the adalimumab pre-filled vials is tested under (b) (4)

*Reviewer's Comments: The sponsor noted that the test for integrity is based on (b) (4)
 A total of 20 vials are tested and (b) (4)
 of any of the vials.*

3.2.P.5.4 Batch Analyses

Adalimumab 50 mg/mL solution for injection, 40 mg/0.8 mL vials batch analyses data for one demonstration batch (81410SP), four commercial scale process validation batches (83433SP, 83443SP, 84457SP and 91070SP) and one post-validation batch (03144LJ) manufactured at (b) (4) are presented below.

Table 1 is a summary of the drug product batches and corresponding drug substance batches used in formulation. Table 2 presents the release testing data for each of the six batches.

Table 1. 40 mg/0.8 mL Vial Drug Product Batches Manufactured at (b) (4)

Drug Product Batch	Drug Substance Batches Used
81410SP	59023BF 59024BF
83433SP	50049BF
83443SP	50049BF 50050BF
84457SP	59027BF
91070SP	50049BF 59027BF
03144LJ	92053A6

Table 2 presents the release testing data for each of the six batches.

Note: Table 3 was obtained from BLA 125057 (b) (4) PAS supplement.

Table 2. Batch Analyses of 40 mg/0.8 mL Vial Drug Product Batches Manufactured at (b) (4)

Test	Specification	Batch					
		81410SP	83433SP	83443SP	84457SP	91070SP	03144LJ
Appearance and Description							
Description	Glass vials with aqueous solution. The vial closure looks intact	Complies	Complies	Complies	Complies	Complies	Complies
Clarity	Not more opalescent than reference suspension (b) (4)	Complies	Complies	Complies	Complies	Complies	Complies (b) (4)
Color	Not more intensely colored than reference solution (b) (4)	Complies	Complies	Complies	Complies	Complies	Complies (b) (4)
Identity							
Adalimumab (Cation exchange HPLC)	The peak pattern complies with that of the characterized reference standard	Complies	Complies	Complies	Complies	Complies	Complies
Purity							
Adalimumab							
- Cation exchange HPLC (b) (4)	(b) (4)	(b) (4)					
- Size exclusion HPLC	(b) (4)	(b) (4)					
- Sterility	No growth appears in the test	Complies	Complies	Complies	Complies	Complies	Complies
	(b) (4)	(b) (4)					
Potency							
Adalimumab							
- In vitro TNF neutralization (b) (4)	(b) (4)	(b) (4)					
Quantity							
Adalimumab							
- Protein content (UV 280 nm)	(b) (4)	(b) (4)					
General Tests							
- pH	(b) (4)	(b) (4)					
- Osmolarity	(b) (4)	(b) (4)					
Pharmaceutical Tests							
- Particulate Matter Visible particles (b) (4)	The solution must be essentially free from particles. The solution must meet the requirements for small volume injections (b) (4)	Complies	Complies	Complies	Complies	Complies	Complies
	(b) (4)	Complies	Complies	Complies	Complies	Complies	Complies (b) (4)
		(b) (4)					
- Volume in Container	Test 5 containers. The volume measured for (b) container is not less than the labeled volume.	Complies	Complies	Complies	Complies	Complies	Complies

Table 3. Batch Analyses of ABL SVP Pre-Filled Syringe Drug Product Registration Run and Product Validation Batches Compared to (b) (4) Batches

Reg. Batch 94005A6	Reg. Batch 94026A6	Reg. Batch 94027A6	PV Batch 95042A6	PV Batch 95025A6	PV Batch 95052A6	PV Batch 95029A6	PV Batch 03170A6	PV Batch 04104A6	PV Batch 05041A6	Vetter Batches (n = 328)
Appearance										
Description: Pre-filled syringes with aqueous solution										
Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	All Comply
Clarity: Not more opalescent than reference suspension (b) (4)										
(b) (4)										
Color: Not more intensely colored than reference solution (b) (4)										
(b) (4)										
Identity										
Cation Exchange HPLC: The peak pattern complies with that of the characterized reference standard										
Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	All Comply
Purity										
Cation Exchange HPLC: (b) (4)										
(b) (4)										
Size Exclusion HPLC: (b) (4)										
(b) (4)										
Purity (continued)										
Sterility: Formulated Drug Product: No growth appears in the test										
Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	All Comply
Sterility: Filled Drug Product: No growth appears in the test										
Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	All Comply
Purity, (b) (4)										
(b) (4)										
Potency										
In vitro TNF Neutralization: (b) (4)										
(b) (4)										
Quantity										
Protein Content (UV 280 nm): (b) (4)										
(b) (4)										
General Tests										
pH: (b) (4)										
(b) (4)										
Osmolality: (b) (4)										
(b) (4)										
Pharmaceutical Tests										
Particulate Matter Visible Particles: The solution must be essentially free from visible particles										
Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	All Comply
Particulate Matter Sub-visible Particles: The solution must meet the requirements for small volume injections										
(b) (4)										
Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	All Comply
(b) (4)										
Volume in Container: The volume measured for each container is not less than the labeled volume. Test 5 containers										
Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	All Comply
0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	All 0.8

a. Data range

(b) (4)

Reviewer’s Comments: *The sponsor didn’t provide any historical data for adalimumab DP in pre-filled syringe (PFS) format produced by the approved (b) (4) PFS facilities, (b) (4) or the small volume parenteral (SVP) facility at Abbott Biotechnology Ltd. (ABL), Puerto Rico.*

I compared the vial release data to 1) batch analysis data for the ABL SVP PFS registration and process validation batches as shown in Table 3 above, as well as 2) the ranges of PFS release data from 328 batches produced at the (b) (4) (b) (4) between July 2008 and December 2010 . These data were submitted for BLA 125057, (b) (4) PAS supplement to obtain approval for the SVP facility as an alternative manufacturing site for adalimumab drug product in pre-filled syringes at the ABL site in Barceloneta, Puerto Rico.

I found that release testing results (Table 2) of batches for all adalimumab in vial format produced at (b) (4) are comparable to those for adalimumab in PFS format produced at approved facilities for the adalimumab in PFS format (Table 3).

Lower levels of (b) (4) are observed adalimumab in the vial than in the pre-filled syringe. The lower level is a result of less (b) (4) in the vial format, which has (b) (4) present only on the stopper and not on the glass surface.

These are acceptable.

3.2.P.7 Container Closure System

The Container Closure System section contains information on the primary packaging (b) (4) glass vial, (b) (4) stopper and (b) (4) cap. There have been **no changes to the product contact surfaces**. However, the original (v) (4) stopper has been changed from a (b) (4) stopper, (b) (4) stopper, also (b) (4)

Table 1. Primary Package Components for Adalimumab 50 mg/mL Solution for Injection in Pre-filled Vials

Component	Description
Primary Packaging	(b) (4)
Glass vial	
(b) (4) stopper	(b) (4)
(b) (4) cap	(b) (4) cap (b) (4)

Reviewer’s Note: *The sponsor has used comparable primary packaging materials with the primary difference of replacing the original (b) (4) stopper with a (b) (4) stopper – both are (b) (4)*

To support this change, the sponsor provided data from forced extraction studies. These studies were performed with syringe plunger stoppers made of the same (b) (4) (b) (4) the same (b) (4) of the syringe plunger stopper) as for the vial (b) (4) stoppers used to manufacture bulk prefilled vials at (b) (4).

A risk-based approach was employed to select a subset of the extractable substances detected after forced extraction for method validation and potentially leachable impurities evaluation in actual (pre-filled syringe) product samples. This risk assessment utilized a ranking system for each extractable compound based on the relevance of the solvent in which it was extracted, the amount of the extractable detected, and the relative toxicological properties of the compound as indicated by its acceptable daily intake (ADI) value.

The full list of compounds validated and tracked as potentially leachable impurities and the analytical methods used to detect them is shown in Table 4.

Table 4. Test Methods and Analytes

Method Type	Analyte
HPLC	(b) (4)
GC-FID Headspace	(b) (4)
GC-MS	(b) (4)
ICP Spectrometry	(b) (4)

Samples from pre-filled syringe batches with (b) (4) needles (b) (4), which were filled using (b) (4) plunger stoppers and stored at the recommended storage temperature of 2° to 8°C, were evaluated for the detection of any leachables using HPLC, GC/MS, Headspace GC-FID, and ICP Spectrometry by (b) (4) at time points ranging from Time 0 through 18 months. All results indicated that there was no change to the potentially leachable impurities from the initial time point to the 18 month time point.

All results were below the method detection limits or the method quantitation limits.

Reviewer's Comments: These are acceptable.

3.2.P.8 Stability

The proposed shelf-life for the vial presentation of Humira is 24 months. This is the same as the currently approved shelf-life for the pre-filled syringe presentation.

Stability of adalimumab 50 mg/mL solution for injection, 40 mg/0.8 mL vial manufactured at the (b) (4) is summarized in the Stability Assessment Report D 020038. The complete stability report for the (b) (4) validation batches is in Stability Data-D013819E07.

Stability protocol is listed in Table 1 and acceptance criteria listed in Table 2.

Table 1. Stability Sampling Protocol, Adalimumab 40 mg/0.8 mL Pre-Filled Vials

Storage Conditions	0	3	6	9	12	18	24	36
5°C	XYZ	X	XZ ¹	X	XZ	X	XYZ	XYZ
25°C/60%RH		X	X	-	-	-	-	-
40°C/75%RH		X	X	-	-	-	-	-

X = Clarity, Color, Cation Exchange HPLC, SEC, *In vitro* TNF neutralization, Protein Content, pH, Visible (b) (4)
 Y = (b) (4)
 Z = Container Closure Integrity.

Stability data for the subsequent time points will be submitted on availability in the annual reports to the BLA.

Table 2. Stability Testing Requirements, Adalimumab 50 mg/mL Solution for Injection, in 40 mg /0.8 mL Pre-filled Vials

Test	Acceptance criteria	Reference to analytical procedures
Appearance and description		(b) (4)
Clarity	Not more opalescent than reference suspension (b) (4)	
Color	Not more intensely colored than reference solution (b) (4)	
Identity		(b) (4)
- Adalimumab (cation exchange HPLC)	The peak pattern complies with that of the characterized reference standard	
Purity		
Adalimumab		
- Cation exchange HPLC		(b) (4)
	(b) (4)	
SDS Gel electrophoresis (for information only)		(b) (4)
- Reduced		
- Purity		
- Non reduced		
- Purity		(b) (4)
- Size exclusion HPLC	(b) (4)	
Potency		
Adalimumab		(b) (4)
- In vitro TNF neutralization		
	(b) (4)	
Quantity		
Adalimumab		(b) (4)
- Protein content (UV 280 nm)		
General tests		
- pH		
Pharmaceutical tests		
- Particulate Matter		(b) (4)
Visible particles	The solution must be essentially free from visible particles	
Sub-visible particles	The solution must meet the requirements for small volume injections (b) (4)	
Container closure integrity		(b) (4)
	Test 20 containers	

One demonstration batch (81410SP), four process validation batches (83433SP, 83443SP, 84457SP and 91070SP), and a post-validation batch (03144LJ) of adalimumab 40 mg, solution for injection in 0.8 mL vials, stoppered with (b) (4) stoppers, (b) (4) (b) (4), were manufactured at the (b) (4) site in (b) (4) and placed on stability to confirm acceptable stability of drug product.

Batch no.	Manuf. date	Drug substance used	Drug substance characteristics	Study start	Storage conditions and testing times	Remarks/ purpose	SSR no.	Available data (months)
81410SP	Sep 2009	59023BF 59024BF	(b) (4)	14-10-09	5°C: 0,3,6,9,12, 18,24,36M +25, +40°C: 3,6M	Demo vial batch – (b) (4)	D018200	24
83433SP	Nov 2009	50049BF	(b) (4)	30-11-09	5°C: 0,3,6,9,12, 18,24,36M +25, +40°C: 3,6M	Process validation vial batch (b) (4)	D018125	24
83443SP	Nov 2009	50049BF 50050BF	(b) (4)	16-12-09	5°C: 0,3,6,9,12, 18,24,36M +25, +40°C: 3,6M	Process validation vial batch (b) (4)	D018125	24
84457SP	Dec 2009	59027BF	(b) (4)	18-01-10	5°C: 0,3,6,9,12, 18,24,36M +25, +40°C: 3,6M	Process validation vial batch (b) (4)	D018125	24
91070SP	Jul. 10	50049BF 59027BF	(b) (4)	06-09-10	5°C: 0,3,6,9,12, 18,24,36M +25, +40°C: 3,6M	Process validation vial batch (b) (4)	D018323	18
03144LJ	Mar 11	92053A6	(b) (4)	30-3-11	5°C: 0,3,6,9,12, 18,24,36M +25, +40°C: 3,6M	First commercial vial lot	D019349	12

Reviewer's Comments: In this submission, stability data for adalimumab 50 mg/mL solution for injection, 40 mg/0.8 mL vial manufactured at (b) (4) were provided as:

- 24 months for the demonstration lot (batch 81410SP) and three process validation lots (batches 83433SP, 83443SP and 84457SP)
- 18 months for the fourth 2010 validation lot (batch 91070SP)
- 12 months for the post-validation lot (batch 03144LJ)

The sponsor noted that all stability data at the long-term storage condition of 2 to 8°C are within specification.

Throughout the period tested, none of the stability batches stored at 5°C showed any significant changes with regard to clarity, pH, visible particles, (b) (4), in vitro TNF neutralization, protein content, container closure integrity testing, and microbiological quality.

The results of these stability studies supports that adalimumab 40 mg solution for injection 0.8 mL, stored in (b) (4) glass vials with (b) (4) stoppers (b) (4) (formulation) is stable for at least 24 months when stored at 2 to 8°C.

These are acceptable.

A summary of the results obtained for the stability-indicating size exclusion HPLC (SE-HPLC), in vitro TNF neutralization and cation exchange HPLC (CEX HPLC) assays for the vial batches is presented in Table 1 through Table 6.

Size Exclusion HPLC (SE-HPLC)

A typical chromatogram of SE-HPLC is shown in Figure 1.

Figure 1: Typical SE-HPLC chromatogram of adalimumab drug product stored for 3 months at 5, 25 and 40°C



Table 1. Comparison of SE-HPLC Stability Data for Vials Registration and Process Validation Lots to (b) (4) PFS Process Validation Lots

Test	Shelf Life Specification	Lot	S20099A (PFS)			S20169A (PFS)			S30279A (PFS)											
			+5°C	+25°C/ 60%RH	+40°C/ 75%RH	+5°C	+25°C/ 60%RH	+40°C/ 75%RH	+5°C	+25°C/ 60%RH	+40°C/ 75%RH									
SE-HPLC	(b) (4)	Initial	(b) (4)																	
		3																		
		6																		
		9																		
		12																		
		18																		
		24																		
		Lot										S3433SP (Vial) *	S3443SP (Vial) *	S4457SP (Vial) *						
		Initial										(b) (4)								
		3																		
		6																		
		9																		
		12																		
		18																		
24																				

Test	Shelf Life Specification	Lot	81410SP (Vial) *			91070SP (Vial) *			03144LJ (Vial) *													
			+5°C	+25°C/ 60%RH	+40°C/ 75%RH	+5°C	+25°C/ 60%RH	+40°C/ 75%RH	+5°C	+25°C/ 60%RH	+40°C/ 75%RH											
SE-HPLC	(b) (4)	Initial	(b) (4)																			
		3																				
		6																				
		9																				
		12																				
		18																				
		24																				
												(b) (4)										

Cation Exchange HPLC (CEX-HPLC)

Figure 3 shows a typical chromatogram, representative of adalimumab samples in these studies, stored for 3 months at 5°C and also under accelerated (25°C) and stressed (40°C) conditions.

Figure 3: Typical CEX-HPLC chromatograms of adalimumab solution for injection stored for 3 months at 5, 25 or 40°C



Table 3. Comparison of CEX Sum of (b) (4) Stability Data for Vials Registration and Process Validation Lots to (b) (4) PFS Process Validation Lots

Test	Shelf Life Specification	Lot	S20099A (PFS)			S20169A (PFS)			S30279A (PFS)											
			+5°C	+25°C/ 60%RH	+40°C/ 75%RH	+5°C	+25°C/ 60%RH	+40°C/ 75%RH	+5°C	+25°C/ 60%RH	+40°C/ 75%RH									
CEX HPLC	(b) (4)	Interval (month)	(b) (4)																	
		Initial																		
		3																		
		6																		
		9																		
		12																		
		18																		
		24																		
		Lot										83433SP (Vial) *	83443SP (Vial) *	84457SP (Vial) *						
		Initial										(b) (4)								
		3																		
		6																		
		9																		
		12																		
18																				
24																				
			S1410SP (Vial) *			91070SP (Vial) *			03144LJ (Vial) *											
			+5°C	+25°C/ 60%RH	+40°C/ 75%RH	+5°C	+25°C/ 60%RH	+40°C/ 75%RH	+5°C	+25°C/ 60%RH	+40°C/ 75%RH									
CEX HPLC	(b) (4)	Interval (month)	(b) (4)																	
		Initial																		
		3																		
		6																		
		9																		
		12																		
		18																		
		24																		
			(b) (4)																	

Table 4. Comparison of CEX (b) (4) Stability Data for Vials Registration and Process Validation Lots to (b) (4) PFS Process Validation Lots

Test	(b) (4)	Lot	520099A (PFS)			520169A (PFS)			530279A (PFS)				
			Interval (month)	+5°C	+25°C/ 60%RH	+40°C/ 75%RH	+5°C	+25°C/ 60%RH	+40°C/ 75%RH	+5°C	+25°C/ 60%RH	+40°C/ 75%RH	
CEX HPLC	(b) (4)	Initial	(b) (4)										
		3											
		6											
		9											
		12											
		18											
		24											
				Lot	83433SP (Vial) *			83443SP (Vial) *			84457SP (Vial) *		
				Initial	(b) (4)								
		3											
		6											
		9											
		12											
18													
24													

* Inverted vial stability data used for this batch

Table 5. Comparison of (b) (4) Stability Data for Vials Registration and Process Validation Lots to (b) (4) PFS Process Validation Lots

Test	(b) (4)	Lot	520099A (PFS)			520169A (PFS)			530279A (PFS)				
			Interval (month)	+5°C	+25°C/ 60%RH	+40°C/ 75%RH	+5°C	+25°C/ 60%RH	+40°C/ 75%RH	+5°C	+25°C/ 60%RH	+40°C/ 75%RH	
CEX HPLC	(b) (4)	Initial	(b) (4)										
		3											
		6											
		9											
		12											
		18											
		24											
				Lot	83433SP (Vial) *			83443SP (Vial) *			84457SP (Vial) *		
				Initial	(b) (4)								
		3											
		6											
		9											
		12											
18													
24													

* Inverted vial stability data used for this batch

Table 6. Comparison of CEX Peak between (b) (4) Stability Data for Vials Registration and Process Validation Lots to (b) (4) PFS Process Validation Lots

Test	(b) (4)	Lot	S20099A (PFS)			S20109A (PFS)			S30279A (PFS)		
			Interval (month)	+5°C	+25°C/ 60%RH	+40°C/ 75%RH	+5°C	+25°C/ 60%RH	+40°C/ 75%RH	+5°C	+25°C/ 60%RH
CEX HPLC	(b) (4)	Initial	(b) (4)								
		3	(b) (4)								
		6	(b) (4)								
		9	(b) (4)								
		12	(b) (4)								
		18	(b) (4)								
		24	(b) (4)								
		Lot	83433SP (Vial) *			83443SP (Vial) *			84467SP (Vial) *		
		Initial	(b) (4)								
		3	(b) (4)								
		6	(b) (4)								
		9	(b) (4)								
		12	(b) (4)								
		18	(b) (4)								
24	(b) (4)										
Test	(b) (4)	Lot	81410SP (Vial) *			91070SP (Vial) *			03144LJ (Vial) *		
		Interval (month)	+5°C	+25°C/ 60%RH	+40°C/ 75%RH	+5°C	+25°C/ 60%RH	+40°C/ 75%RH	+5°C	+25°C/ 60%RH	+40°C/ 75%RH
CEX HPLC	(b) (4)	Initial	(b) (4)								
		3	(b) (4)								
		6	(b) (4)								
		9	(b) (4)								
		12	(b) (4)								
		18	(b) (4)								
		24	(b) (4)								

* Inverted vial stability data used for this batch

In-vitro TNF neutralization assays

Table 2. Comparison of *In Vitro* TNF Neutralization Stability Data for Vials Registration and Process Validation Lots to (b) (4) PFS Process Validation Lots

Test	(b) (4)	Lot	520099A (PFS)			520169A (PFS)			530279A (PFS)		
			Interval (month)	+5°C	+25°C/ 60%RH	+40°C/ 75%RH	+5°C	+25°C/ 60%RH	+40°C/ 75%RH	+5°C	+25°C/ 60%RH
In vitro TNF Neutralization	(b) (4)	Initial	(b) (4)								
		3									
		6									
		9									
		12									
		18									
		24									
		Lot	83433SP (Vial) *	83443SP (Vial) *			84457SP (Vial) *				
		Initial	(b) (4)								
		3									
		6									
		9									
		12									
		18									
24											

Test	(b) (4)	Lot	81410SP (Vial) *			91070SP (Vial) *			03144LJ (Vial) *		
			Interval (month)	+5°C	+25°C/ 60%RH	+40°C/ 75%RH	+5°C	+25°C/ 60%RH	+40°C/ 75%RH	+5°C	+25°C/ 60%RH
In vitro TNF Neutralization	(b) (4)	Initial	(b) (4)								
		3									
		6									
		9									
		12									
		18									
		24									
		Lot	81410SP (Vial) *			91070SP (Vial) *			03144LJ (Vial) *		
		Initial	(b) (4)								
		3									
		6									
		9									
		12									
		18									
24											

* Inverted vial stability data used for this batch

Reviewer's Comments: *The sponsor claimed in the submission that the available vial stability data (i.e., from SE-HPLC, CEX-HPLC, and In-vitro TNF neutralization assays) show product stability trends, at recommended storage condition at 2 to 8°C as well as at accelerated and stressed storage conditions, that are comparable to PFS batches produced by the approved DP facilities. There are no significant differences in the trends observed for clarity, color, protein content, pH, and visible particles.*

I agree with the sponsor's claim.

*The sponsor also noted in the submission that stability data for the subsequent time points will be submitted on availability in the **annual reports to the BLA.***

These are acceptable.

Comment by L. Graham: *The data provided support the proposed 24 months shelf-life for the vial DP.*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JUN T PARK
04/10/2013

LAURIE J GRAHAM
04/10/2013

PATRICK G SWANN
04/12/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125057Orig1s322

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW

Division of Pulmonary, Allergy, and Rheumatology Products

Application Number: sBLA 125057/322
Name of Drug: Humira™ (adalimumab)
Applicant: AbbVie Inc.
Submission Date: November 16, 2012
Receipt Date(s): November 16 2012
Type of Labeling Reviewed: WORD/SPL

Background and Summary

This Prior Approval Supplement submitted on November 16, 2012, proposes for a revision to the “Dosage Forms and Strengths” section of the package insert for the addition of the 40 mg single dose vial for institutional use only.

Review

The most recent approved label dated January 31, 2013, was compared to the proposed labeling submitted on November 16, 2012.

The following revisions were noted:

Highlights Section (HL)

- The Recent Major Changes: the following sentence was added:
 - “Dosage and Administration, General Considerations for Administration (2.7) ----- MM/YYYY”
- Dosage Forms and Strengths, the following bullet was added:
 - Injection: 40 mg/0.8 ml in a single-use glass vial for institutional use only (3)

Full Prescribing Information (FPI)

- Section 2, Dosage and Administration, Subsection 2.7, General Considerations for Administration, the following statement was added:
 - The HUMIRA institutional use vial is for use and administration within an institutional setting only, such as a hospital, physician's office or clinic. Withdraw the dose using a sterile needle and syringe and administer promptly by a healthcare provider within an

institutional setting. Only administer one dose per vial. The vial does not contain preservatives; therefore, discard unused portions.

- Section 3, Dosage Forms and Strengths, the following bullet was added:
 - Institutional Use Vial

Injection: A single-use, glass vial, providing 40 mg (0.8 ml) of HUMIRA for institutional use only.

- Section 16, How Supplied/Storage and Handling, the following bullet was added:
 - Institutional Use Vial Carton-40 mg

HUMIRA is supplied for institutional use only in carton containing a single-use, glass vial, providing 40 mg (0.8 ml) of HUMIRA. The NDA number is 0074-3797-01.
 - Also under the section, the words [REDACTED] (b) (4) was deleted from the sentence.

Other revisions noted includes sponsor's name change throughout the label, in which the former sponsor, Abbott, had transferred license ownership of Humira to the new sponsor, AbbVie Inc. An official letter of the license transfer was communicated to the sponsor on January 31, 2013.

Also during the review, the revision date was not updated to reflect the current month of approval date (pending) and that the revised date at the end of the Full Prescribing Information should be deleted. The sponsor will be notified and requested that the label be updated to reflect the above.

This supplement is also reviewed by the clinical reviewer, Sarah Yim, M.D, on April 17, 2013, Products reviewer, Jun Park, Ph.D., on April 12, 2013, OBP Reviewer, Kimberly Rains, Pharm.D., on April 02, 2013, and DMEPA Reviewer, Teresa McMillan, Pharm.D., on March 21, 2013, and recommended for approval.

Recommendations

I agree that the revisions noted above and submitted in the labeling dated November 16, 2012, are the only changes compared to that approved on January 31, 2013, with the a few differences noted above which will be conveyed to the sponsor. I recommend approval of the supplement.

Sadaf Nabavian, Pharm.D.
Regulatory Project Manager

Supervisory Comment/Concurrence:

Ladan Jafari
Chief, Project Management Staff

Drafted: SNabavian/03.25.2013

Cleared: LJafari/03.28.2013

Finalized: SNabavian/04.19.2013

Filename: CSO Labeling Review Template (updated 1-16-07).doc

CSO LABELING REVIEW

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SADAF NABAVIAN
04/19/2013

LADAN JAFARI
04/19/2013



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Federal Research Center
Tel. 301-796-4242

FINAL LABEL AND LABELING REVIEW

Date: April 2, 2013

Reviewer: Kimberly Rains, Pharm.D.
Labeling Reviewer
Office of Biotechnology Products

Through: Jun Park, Ph.D.
Product reviewer
Division of Monoclonal Antibodies

Kathleen A. Clouse, Ph.D.
Director
Division of Monoclonal Antibodies

Application: STN 125057/322

Product: HUMIRA[®] (adalimumab)

Applicant: AbbVie Inc.

Submission Date(s): November 16, 2012, March 18, 2013

Executive Summary:

The carton and container for HUMIRA[®] (adalimumab) were reviewed and found to conform to the applicable regulations under 21 CFR 201 Subpart A and 21 CFR 610 – Subpart G.

Background:

Abbott Laboratories submitted a supplement to HUMIRA[®] (adalimumab), BLA 125057, to reintroduce an institutional only presentation of the 40 mg /0.8 mL vial. Humira was initially approved with four drug product presentations that included both prefilled syringes and vials. The vial presentations were removed from the market and replaced with self-administration configurations including a prefilled syringe and a pen. The applicant has proposed to market a vial presentation for institutional use only (health care provider administration only). This new presentation would prevent additional out of

pocket cost for patients who have been prescribed Humira therapy but need a health care provider to administer their injections because they may find it difficult to access the drug and follow the prescribed course of treatment. Some medical benefits specify that any cost incurred by the patient for administration of Humira by a health care provider is not covered because the drug is approved for self-administration only.

Information Reviewed:

HUMIRA[®] (adalimumab) -Vial presentation 40 mg/0.8 mL

<http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea68111de09>

Sequence: 0176, 0195

REVIEW

Start of sponsor material

(b) (4)



(b) (4)



End of sponsor material

Conclusions:

The Division of Medication Error Prevention and Analysis submitted minor recommendations for the labels submitted on November 16, 2012. The revised vial and carton label for institutional use submitted March 18, 2013 are acceptable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLY M RAINS
04/02/2013

JUN T PARK
04/02/2013

KATHLEEN A CLOUSE STREBEL
04/02/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling, and Packaging Review Memo

Date: March 21, 2013

Reviewer(s): Teresa McMillan, PharmD
Division of Medication Error Prevention & Analysis

Team Leader: Lubna Merchant, PharmD
Division of Medication Error Prevention & Analysis

Drug Name(s) and Strength(s): Humira (Adalimumab)
Injection
40 mg/0.8 mL Vial

Application Type/Number: BLA/125057

Submission Number: 322

Applicant/sponsor: Abbott Laboratories, Inc

OSE RCM #: 2012-2907-1

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1	Introduction.....	3
2	Methods and Materials Reviewed.....	3
3	Conclusions and Recommendations	3
	References.....	4
	Appendix.....	5

1 INTRODUCTION

This review evaluates the revised 40 mg/0.8 mL Humira (adalimumab) container labels and carton labeling submitted by the Applicant in response to the Division of Medication Error Prevention and Analysis's (DMEPA's) previous comments in OSE Review #2012-2907, dated March 7, 2013.

2 METHODS AND MATERIALS REVIEWED

The revised container labels and carton labeling submitted to the FDA on March 18, 2013 (See Appendix A for images of the container labels and carton labeling) and OSE Review #2012-2907, dated March 7, 2013, were evaluated to assess whether the revisions adequately address our concerns from a medication error perspective.

3 CONCLUSIONS AND RECOMMENDATIONS

The revised container labels and carton labeling addressed all of DMEPA's concerns and we have no additional comments.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Nichelle Rashid, at 301-796-3904.

REFERENCES

1. OSE Review #2012-2907-1, Label, Labeling, and Packaging Review for Humira, March 7, 2013, McMillan,T.

2 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TERESA S MCMILLAN
03/21/2013

LUBNA A MERCHANT
03/21/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: March 7, 2013

Reviewer(s): Teresa McMillan, PharmD
Division of Medication Error Prevention & Analysis

Team Leader: Lubna Merchant, PharmD
Division of Medication Error Prevention & Analysis

Associate Director: Scott Dallas, RPh
Division of Medication Error Prevention & Analysis

Drug Name(s) and Strength(s): Humira (Adalimumab)
Injection
40 mg/0.8 mL Vial

Application Type/Number: BLA/125057

Submission Number: 322

Applicant/sponsor: Abbott Laboratories, Inc

OSE RCM #: 2012-2907

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1	Introduction.....	3
1.1	Background.....	3
1.2	Product Information.....	3
2	Methods and Materials Reviewed.....	4
2.1	Labels and labeling.....	4
3	Integrated Summary of Medication error risk assesment.....	4
4	Conclusions.....	4
5	Recommendations.....	5
	Appendices.....	6

1 INTRODUCTION

This review evaluates the proposed container label, insert and carton labeling for Humira (adalimumab), BLA 125057 for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND

On November 16, 2012, the Applicant submitted a prior approval supplement to the Agency to reintroduce the single-use Humira 40 mg/0.8 mL vial for institutional use only. Humira is currently approved to treat Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Crohn's Disease, Ankylosing Spondylitis, Psoriatic Arthritis and Plaque Psoriasis and supplied in the following strengths and product presentations: 20 mg/0.4 mL single-use pre-filled syringe, 40 mg/0.8 mL single-use pre-filled syringe and 40 mg/0.8 mL single-use autoinjector.

The Applicant's rationale for proposing the reintroduction of the single-use Humira 40 mg/0.8 mL vial include the fear of self-administration and physical disabilities for clinically appropriate candidates for Humira therapy. In addition, patients who have been prescribed Humira may require healthcare practitioners for administration for the aforementioned reasons, but may find it difficult due to their medical coverage benefit design which specifies that any costs incurred by the patient for administration of Humira by a healthcare practitioner are not covered because the drug is approved for self-administration only.

1.2 PRODUCT INFORMATION

The following product information is provided in the November 16, 2012 proprietary name submission.

- Active Ingredient: Adalimumab
- Indication of Use: Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Crohn's Disease, Ankylosing Spondylitis, Psoriatic Arthritis and Plaque Psoriasis, Ulcerative Colitis
- Route of Administration: Subcutaneous
- Dosage Form: Solution
- Strength: 20 mg/0.4 mL, 40 mg/0.8 mL, 40 mg/0.8 mL
- Dose and Frequency: 20 mg, 40 mg, 80 mg, or 160 mg every other week
- How Supplied: Single-use Pre-filled syringe, Single-use Pen, Single-use Vial- Institutional use only
- Storage: Refrigerated at 2°C to 8° C (36° to 46° F) and should be protected from exposure to light.

2 METHODS AND MATERIALS REVIEWED

An AERS search was not conducted for this supplement because we have been actively monitoring medication errors with this product. There have been reports of incomplete injection and accidental firing associated with the Humira Pen. The issues have been discussed in OSE Reviews #2012-578, #2001-2102 and #2009-935. This supplement involves the addition of a new vial and does not directly involve the issues discussed above. DMEPA reviewed the Humira labels and package insert labeling submitted by the Applicant.

2.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels, Carton and Insert Labeling submitted on November 16, 2012 (See Appendix B and C for images, no image available for insert labeling)

3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

The Applicant is proposing to reintroduce the single-use Humira 40 mg/0.8 mL vial for institutional use only. This proposed drug presentation is available in the same strength as the currently approved single-use pre-filled syringe and autoinjector presentations and is to be administered via the same route of administration (i.e. subcutaneous). The Applicant has adequately revised the insert labeling to reflect the proposed single-use Humira 40 mg/0.8mL vial in the following sections: Dosage Forms and Strengths and the How Supplied/Storage and Handling. However, the evaluation of the proposed labels and labeling noted that the [REDACTED] (b) (4) [REDACTED] the 40 mg/0.8 mL vial container label. We note that the route of administration is present on the currently approved Humira pre-filled syringe and autoinjector labels and labeling and the single-use statement is only on the blister label and the carton labeling. However, because this proposed drug presentation is a vial and more than one dose could be retrieved, it is prudent to label the container as single-use.

4 CONCLUSIONS

DMEPA concludes that the proposed insert labeling is sufficient. However, the container label and the carton labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this BLA supplement:

5.1 COMMENTS TO THE APPLICANT

A. Container Labels

1. We note that the [REDACTED] (b) (4)
[REDACTED] 40 mg/0.8 mL container label. [REDACTED] (b) (4)
[REDACTED]

2. We note that the [REDACTED] (b) (4)
[REDACTED] 40 mg/0.8 mL container label. The proposed presentation is a vial,
thus more than one dose could be retrieved. Therefore, [REDACTED] (b) (4)
[REDACTED]

B. Carton Labeling

1. The proposed presentation is a vial, thus more than one dose could be
retrieved. Therefore, [REDACTED] (b) (4)
[REDACTED]

2. [REDACTED] (b) (4)
[REDACTED] "One 40 mg Vial".

If you have further questions or need clarifications, please contact Nichelle Rashid, project manager, at 301-796-3904.

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TERESA S MCMILLAN
03/07/2013

LUBNA A MERCHANT
03/07/2013

SCOTT M DALLAS
03/07/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125057Orig1s322

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II**

Memorandum of Facsimile Correspondence

Date: March 15, 2013

To: Gresham Weatherly, Ph.D.
Associate Director, CMC Regulatory Affairs

Phone: (847) 937-78-33

From: Sadaf Nabavian, Pharm.D.
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: Comments re: BLA 125057/322

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 796-2300 and return it to us at FDA, 10903 New Hampshire Ave, Building 22, DPAP, Silver Spring, MD 20993.

Thank you.

BLA 125057/322

Humira
AbbVie Inc.

Dear Dr. Weatherly:

Your submission dated November 16, 2012, is currently under review and we have the following comments and requests for information pertaining to Chemistry, Manufacturing, and Controls for Humira.

1. Provide a justification for the increase in the fill volume for the drug product (DP) in the vial presentation from (b) (4) mL to (b) (4) mL, particularly as the new fill volume would appear to exceed the excess volume recommendations from (b) (4). In addition, provide a justification for the use of only one validation run with the new fill volume.
2. Provide summary information to support the comparability of the vial DP with the pre-filled syringe (PFS). This comparability assessment should include the use of acceptance criteria based on historical release as well as real time, accelerated, and stressed stability data.
3. Provide clarification on any difference in drug product specifications between the vial and PFS DP. For example, it is noted that many of the CEX-HPLC release acceptance criteria for the PFS are listed as “not tested” for the vial DP.
4. Provide additional information and data for validation of the container closure integrity. Include the high and low (b) (4) used on the vials and the (b) (4) stress conditions used in the performance of the test. Describe the sensitivity of the test (minimum detectable leak size) and the positive controls used. Confirm that the media used in the test was tested for growth promotion.
5. Provide a summary of (b) (4). The report should include information on the type and lots of (b) (4) validated the actual number of (b) (4) and recovery data and the (b) (4).
6. Provide a summary of (b) (4) data for (b) (4) used for validation batches.

In order to facilitate the review of your BLA submission, submit your response to me via telephone facsimile to 301-796-9728 or email at Sadaf.Nabavian@fda.hhs.gov by COB, Tuesday March 19, 2013. Your responses will subsequently need to be submitted officially to the BLA. If you have any questions, please contact Sadaf Nabavian, Regulatory Program Manager, at 301-796-2777.

Initial Draft: SNabavian/03.14.2013

Cleared: LJafari/03.15.2013

Finalized: SNabavian/03.15.2013

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SADAF NABAVIAN
03/15/2013

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.1

Instructions:

The review team should upload this form into DARRTS by checking the form in as a communication. The DARRTS “Communication Group” is “BLA Administrative Form” and the “Communication Name” is “FRM-BLAADMIN-61 – Establishment Evaluation Request Form.”

TB-EERs should be submitted:

- 1) within 10 business days of the application filing date (initial TB-EER)
- 2) 15-30 days prior to the planned action date (final TB-EER)

When requesting establishment evaluations, please include only the site (or sites) directly affected by the proposed changes. For efficacy supplements or license transfers, please include all licensed manufacturing sites.

For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

Date: March 1, 2013
To: Administrative File, STN 125057/322
From: Donald C. Obenhuber, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB
Endorsement Patricia F. Hughes, Ph.D., Team Leader,
CDER/OC/OMPQ/DGMPA/BMAB
Subject: PAS: Reintroduction of the 40 mg/0.8 ml vial presentation for institutional use only and to be added to the Dosage Forms and Strengths section of the PI.
Applicant: AbbVie Inc.
US License: 1889
Product: Humira (Adalimumab)
Dosage: 50 mg/mL Solution for Injection, 40 mg/0.8mL Vial
Indication: Rheumatoid Arthritis, JIA, Psoriatic Arthritis, Ankylosing Spondylitis, Crohn's Disease, Plaque Psoriasis, Ulcerative Colitis
PDUFA date: May 18, 2013

FACILITY INFORMATION

Facility:  (b) (4)

This site was inspected by (b) (4) on July 9 – 17, 2012 and classified NAI. This was a routine GMP surveillance inspection covering biotech drug product manufacturing operations. The SVS profile was updated and is acceptable.

OVERALL RECOMMENDATION

There are no ongoing or pending compliance actions that prevent approval of this supplement. Please resubmit this TB-EER 15-30 days prior to the planned action date for an updated compliance evaluation.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RANJANI PRABHAKARA
03/08/2013



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II**

Memorandum of Facsimile Correspondence

Date: March 7, 2013

To: Gresham Weatherly, Ph.D.
Associate Director, CMC Regulatory Affairs

Phone: (847) 937-78-33

From: Sadaf Nabavian, Pharm.D.
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: Comments re: BLA 125057/322

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 796-2300 and return it to us at FDA, 10903 New Hampshire Ave, Building 22, DPAP, Silver Spring, MD 20993.

Thank you.

BLA 125057/322

Humira

AbbVie Inc.

Dear Dr. Weatherly:

Your submission dated November 16, 2012, is currently under review and we have the following comments and requests for information pertaining to the carton and container labels for Humira. Please note that these comments are not necessarily our final comments and that we may have additional labeling recommendations as we continue to review your application.

Container Label

1. We note that the route of administration (b) (4)
[REDACTED]
2. We note that the “single-use” statement (b) (4)
[REDACTED] The proposed presentation is a vial,
thus more than one dose could be retrieved. Therefore (b) (4)
[REDACTED]

Carton Label

1. The proposed presentation is a vial, thus more than one dose could be retrieved. Therefore, (b) (4)
[REDACTED]
2. Revise the net quantity statement from (b) (4) to appear as “One 40 mg Vial”.

In order to facilitate the review of your BLA submission, submit your response to me via telephone facsimile to 301-796-9728 or email at Sadaf.Nabavian@fda.hhs.gov by COB, Thursday, March 14, 2013. Your responses will subsequently need to be submitted officially to the BLA. If you have any questions, please contact Sadaf Nabavian, Regulatory Program Manager, at 301-796-2777.

Initial Draft: SNabavian/03.07.2013

Cleared: LJafari/03.07.2013

Finalized: SNabavian/03.07.2013

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SADAF NABAVIAN
03/07/2013

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.1

Instructions:

The review team should upload this form into DARRTS by checking the form in as a communication. The DARRTS "Communication Group" is "BLA Administrative Form" and the "Communication Name" is "FRM-BLAADMIN-61 – Establishment Evaluation Request Form."

TB-EERs should be submitted:

- 1) within 10 business days of the application filing date (initial TB-EER)
- 2) 15-30 days prior to the planned action date (final TB-EER)

When requesting establishment evaluations, please include only the site (or sites) directly affected by the proposed changes. For efficacy supplements or license transfers, please include all licensed manufacturing sites.

For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

Date: March 1, 2013
To: Administrative File, STN 125057/322
From: Donald C. Obenhuber, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB
Endorsement Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB
Subject: PAS: Reintroduction of the 40 mg/0.8 ml vial presentation for institutional use only and to be added to the Dosage Forms and Strengths section of the PI.
Applicant: AbbVie Inc.
US License: 1889
Product: Humira (Adalimumab)
Dosage: 50 mg/mL Solution for Injection, 40 mg/0.8mL Vial
Indication: Rheumatoid Arthritis, JIA, Psoriatic Arthritis, Ankylosing Spondylitis, Crohn's Disease, Plaque Psoriasis, Ulcerative Colitis
PDUFA date: May 18, 2013

FACILITY INFORMATION

Facility:

(b) (4)

OVERALL RECOMMENDATION

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DONALD C OBENHUBER
03/01/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (<i>Division/Office</i>): Mail: OSE		FROM: Sadaf Nabavian, Pharm. D. Regulatory Project Manager, DPAPR, 301-796-2777		
DATE December 06, 2012	IND NO.	BLA NO: BLA125057 STN322	TYPE OF DOCUMENT Prior Approval Supplement	DATE OF DOCUMENT November 16, 2012
NAME OF DRUG Adalimumab	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG TNF Blocker	DESIRED COMPLETION DATE March 08, 2013	
NAME OF FIRM: Abbott				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING <input type="checkbox"/> CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input checked="" type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS:				
<p>The submission is requesting revisions to the "Dosage Forms and Strengths" Section of the package insert for BLA 125057 (adalimumab), with the addition of the 40 mg vial for institutional use only. Therefore DPARP is requesting a consult for a labeling review of the package insert. Thank you. The link of the submission is provided below and as well the proposed label is attached to the consult request form.</p> <p><http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea68111de09></p> <p>The submission is Sequence 176, Supp 322. submitted on November 16, 2012.</p>				
SIGNATURE OF REQUESTER Sadaf Nabavian, RPM, 301-796-2777		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SADAF NABAVIAN
12/06/2012



BLA 125057/STN 322

**PRIOR APPROVAL SUPPLEMENT -
ACKNOWLEDGEMENT & FILING**

Abbott Laboratories
200 Abbott Park Road
Abbott Park, IL 60064

Attention: Gresham Weatherly
Associate Director, Regulatory Affairs-PPG

Dear Mr. Weatherly:

We have received your Supplemental Biologics License Application (sBLA) submitted under section 351(k) of the Public Health Service Act for the following:

BLA SUPPLEMENT NUMBER: BLA 125057/STN 322

PRODUCT NAME: Humira (adalimumab)

DATE OF SUBMISSION: November 16, 2012

DATE OF RECEIPT: November 16, 2012

US LICENSE NUMBER: 0043

This prior approval labeling supplemental application proposes the following change(s):
Addition of the 40 mg vial for institutional use only to be added to the "Dosage Forms and Strengths" Section of the package insert.

Unless we notified you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we have filed the application on in accordance with 21 CFR 601.2(a).

The goal date of this application will be May 18, 2013.

CONTENT OF LABELING

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary, Allergy, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

If you have questions, call me, at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Sadaf Nabavian, Pharm.D.
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SADAF NABAVIAN
12/04/2012