

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
BLA 125057/S-280

Trade Name: HUMIRA

Generic Name: adalimumab

Sponsor: AbbVie Inc.

Approval Date: 12/24/2014

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.

Adult 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.

Pediatric Crohn's Disease - Reducing signs and symptoms and inducing and maintaining clinical remission in patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate.

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 azathioprine, 6-mercaptopurine, or methotrexate.

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.

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APPROVAL LETTER



BLA 125057/S-280

SUPPLEMENT APPROVAL

AbbVie Inc.
1 North Waukegan Road
North Chicago, IL 60064

Attention: Paul Hermes, MS
Associated Director, Regulatory Affairs

Dear Mr. Hermes:

Please refer to your Supplemental Biologics License Application (sBLA), dated December 29, 2011, received December 29, 2011, submitted under section 351(a) of the Public Health Service Act for Humira (adalimumab).

We acknowledge receipt of your amendments dated January 11, and February 20, 2012, and October 13, and December 17, 18, and 23, 2014.

The June 26, 2014, submission constituted a complete response to our April 27, 2012, action letter.

This "Prior Approval" supplemental biologics application proposes a change to the Humira storage instructions to allow for room temperature storage up to 77°F (25°C) for the Humira prefilled syringe, pen, and institutional vial presentations.

APPROVAL & LABELING

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, Medication Guide, and Instructions for Use) 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 December 17, 2014, 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. For administrative purposes, designate this submission “**Product Correspondence – Final Printed Carton and Container Labels for approved BLA 125057/S-280.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

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, MD, PhD
Director
Division of Pulmonary, Allergy, and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures: Content of 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
12/24/2014

**CENTER FOR DRUG EVALUATION AND
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OTHER ACTION LETTER(s)



COMPLETE RESPONSE

Our STN: BL 125057/280

Abbott Laboratories
Attention: Dr. Tobias Gerwig
Senior Manager, Regulatory Affairs
Dept. PA77, Bld AP30-1 NE
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Dr. Gerwig:

This letter is in regard to the supplement to your biologics license application, dated December 29, 2011, received December 29, 2011, submitted under section 351 of the Public Health Service Act for Humira[®] (adalimumab).

We acknowledge receipt of your amendments dated January 11, 2012 and February 20, 2012.

This supplement was for the modification of storage instructions to allow limited storage of the Humira pre-filled syringe and Humira pen presentations at room temperature, plus a label change to allow storage of Humira up to 25°C for single period of up to 14 days.

We have completed the review of your supplement and have determined that we cannot approve the supplement in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues:

- 1. Storage of biologic products under controlled room temperature conditions is unusual and there is great concern over the ability of patients to consistently maintain the product within the validated storage temperature ($\leq 25^{\circ}\text{C}$). Provide all available information with regard to how controlled room temperature will be maintained and monitored by the patient such as a mechanism to monitor whether storage conditions have exceeded the recommended temperature limit (e.g. a colorimetric temperature indicator). Include information/data which adequately support that control over the controlled room temperature by the patient is sufficient to assure product will be stored within its validated storage temperature.**
- 2. You have not included an updated medication guide that incorporates your proposed changes to the recommended storage conditions consistent with changes noted in the package insert and patient instructions.**

3. Please provide a risk assessment for temperature excursions beyond controlled room temperature while drug product is under patient control.

We reserve comment on the proposed labeling until the supplement is otherwise adequate. If you revise labeling, your response must include updated 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>.

Within one year after the date of this letter, you are required to resubmit or withdraw the application. If you do not take any of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). A resubmission must fully address all the deficiencies listed, and will start a new review cycle. A partial response to this letter may not be reviewed and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss the steps necessary for approval. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry on *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079744.pdf>)

If you have any questions, please contact the Regulatory Project Manager, Andrew Shiber, at (301) 796-4798.

Sincerely,

Patrick Swann, Ph.D. for
Kathleen A. Clouse, Ph.D.
Director
Division of Monoclonal Antibodies
Office of Biotechnology Products
Office of Pharmaceutical Science
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/

PATRICK G SWANN
04/27/2012

**CENTER FOR DRUG EVALUATION AND
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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.

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, Juvenile Idiopathic Arthritis (1.2) | 9/2014 |
| Indications and Usage, Pediatric Crohn's Disease (1.6) | 9/2014 |
| Dosage and Administration, Juvenile Idiopathic Arthritis (2.2) | 9/2014 |
| Dosage and Administration, Pediatric Crohn's Disease (2.4) | 9/2014 |
| Dosage and Administration, General Considerations for Administration (2.8) | 12/2014 |

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 patients 2 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.
- **Adult 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.
- **Pediatric Crohn's Disease (1.6):** Reducing signs and symptoms and inducing and maintaining clinical remission in patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate.
- **Ulcerative Colitis (UC) (1.7):** 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) (1.8):** 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):

- 10 kg (22 lbs) to <15 kg (33 lbs) 10 mg every other week
- 15 kg (33 lbs) to < 30 kg (66 lbs) 20 mg every other week
- ≥ 30 kg (66 lbs) 40 mg every other week

Adult Crohn's Disease and Ulcerative Colitis (2.3, 2.5):

- 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.

Pediatric Crohn's Disease (2.4):

- 17 kg (37 lbs) to < 40 kg (88 lbs):
 - Initial dose (Day 1): 80 mg (two 40 mg injections in one day)
 - Second dose two weeks later (Day 15): 40 mg
 - Two weeks later (Day 29): Begin a maintenance dose of 20 mg every other week.
- ≥ 40 kg (88 lbs):
 - 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 40 mg injections in one day)
 - Two weeks later (Day 29): Begin a maintenance dose of 40 mg every other week.

Plaque Psoriasis (2.6):

- 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: 10 mg/0.2 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

- *Live vaccines* Avoid use with HUMIRA (5.10, 7.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2014

-----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)

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*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 have 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 patients 2 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 Adult 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 Pediatric Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate.

1.7 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 (14.7)*].

1.8 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 patients 2 years of age and older 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.

| Patients (2 years of age and older) | Dose |
|--|---|
| 10 kg (22 lbs) to <15 kg (33 lbs) | 10 mg every other week (10 mg Prefilled Syringe) |
| 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) |

HUMIRA has not been studied in patients with polyarticular JIA less than 2 years of age or in patients with a weight below 10 kg.

2.3 Adult 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 Pediatric Crohn's Disease

The recommended HUMIRA dose regimen for pediatric patients 6 years of age and older with Crohn's disease (CD) is based on body weight as shown below:

| Pediatric Patients | Induction Dose | Maintenance Dose Starting at Week 4 (Day 29) |
|------------------------------------|--|--|
| 17 kg (37 lbs) to < 40 kg (88 lbs) | <ul style="list-style-type: none"> • 80 mg on Day 1 (administered as two 40 mg injections in one day); and • 40 mg two weeks later (on Day 15) | <ul style="list-style-type: none"> • 20 mg every other week |
| ≥ 40 kg (88 lbs) | <ul style="list-style-type: none"> • 160 mg on Day 1 (administered as four injections in one day or as two 40 mg injections per day for two consecutive days); and • 80 mg two weeks later (on Day 15) (administered as two 40 mg injections in one day) | <ul style="list-style-type: none"> • 40 mg every other week |

2.5 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.

2.6 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.

2.7 Monitoring to Assess Safety

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

2.8 General Considerations for Administration

HUMIRA is intended for use under the guidance and supervision of a physician. A patient may self-inject HUMIRA or a caregiver may inject HUMIRA using either the HUMIRA Pen or prefilled syringe if a physician determines that it is appropriate, and with medical follow-up, as necessary, after proper training in subcutaneous injection technique.

If more comfortable, you may leave HUMIRA at room temperature for about 15 to 30 minutes before injecting. Do not remove the cap or cover while allowing it to reach room temperature. Carefully inspect the solution in the HUMIRA Pen, prefilled syringe, or single-use institutional use vial 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, according to the directions provided in the Instructions for Use [see *Instructions for Use*].

Injections should occur at separate sites in the thigh or abdomen. Rotate injection sites and do not give injections into areas where the skin is tender, bruised, red or hard.

The HUMIRA single-use institutional use vial is for 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.

Injection: A single-use, 1 mL prefilled glass syringe with a fixed 27 gauge ½ inch needle, providing 10 mg/0.2 mL of HUMIRA.

- **Single-Use 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 and new onset tuberculosis infections have been reported in patients receiving HUMIRA, including patients who have previously received treatment for latent or active tuberculosis. Reports included cases of pulmonary and extrapulmonary (i.e., disseminated) 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. Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with HUMIRA. 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 have 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. The potential risk with the combination of azathioprine or 6-mercaptopurine and HUMIRA should be carefully considered.

5.3 Hypersensitivity Reactions

Anaphylaxis and angioneurotic edema have been reported 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 (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed.

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 pediatric 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 conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in 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 a controlled Phase 3 trial of HUMIRA in patients with polyarticular JIA who were 4 to 17 years, ALT elevations $\geq 3 \times$ ULN occurred in 4.4% of HUMIRA-treated patients and 1.5% of control-treated patients (ALT more common than AST); 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. No ALT elevations $\geq 3 \times$ ULN occurred in the open-label study of HUMIRA in patients with polyarticular JIA who were 2 to <4 years.

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 adult patients with CD with a 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 the Phase 3 trial of HUMIRA in pediatric patients with Crohn's disease which evaluated efficacy and safety of two body weight based maintenance dose regimens following body weight based induction therapy up to 52 weeks of treatment, ALT elevations $\geq 3 \times$ ULN occurred in 2.6% (5/192) of patients, of whom 4 were receiving concomitant immunosuppressants at baseline; none of these patients discontinued due to abnormalities in ALT tests. 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 ≥ 3

x 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 ≥ 3 x 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 polyarticular JIA who were 4 to 17 years of age, 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 polyarticular JIA who were 2 to <4 years of age or 4 years of age and older weighing <15 kg, adalimumab antibodies were identified in 7% (1 of 15) of HUMIRA-treated patients, and the one patient was receiving concomitant MTX.

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

In pediatric patients with Crohn's disease, the rate of antibody development in patients receiving HUMIRA was 3%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 32% of total patients studied), the immunogenicity rate was 10%.

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 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/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 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/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 (N=705) | Placebo (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 patients in the polyarticular juvenile idiopathic arthritis (JIA) trials (Studies JIA-I and JIA-II) 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.

In Study JIA-I, HUMIRA was studied in 171 patients who were 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, and 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.

In Study JIA-I, 45% of patients 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 polyarticular JIA patients who are not treated with TNF blockers. Upon initiation of treatment, the most common adverse reactions occurring in this patient population treated with HUMIRA were injection site pain and injection site reaction (19% and 16%, respectively). A less commonly reported adverse event in patients receiving HUMIRA was granuloma annulare which did not lead to discontinuation of HUMIRA treatment.

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

In Study JIA-I, 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 patients treated with HUMIRA developed mild-to-moderate elevations of creatine phosphokinase (CPK) in Study JIA-I. 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.

In Study JIA-II, HUMIRA was studied in 32 patients who were 2 to <4 years of age or 4 years of age and older weighing <15 kg with polyarticular JIA. The safety profile for this patient population was similar to the safety profile seen in patients 4 to 17 years of age with polyarticular JIA.

In Study JIA-II, 78% of patients experienced an infection while receiving HUMIRA. These included nasopharyngitis, bronchitis, upper respiratory tract infection, otitis media, and were mostly mild to moderate in severity. Serious infections were observed in 9% of patients receiving HUMIRA in the study and included dental caries, rotavirus gastroenteritis, and varicella.

In Study JIA-II, non-serious allergic reactions were observed in 6% of patients and included intermittent urticaria and rash, which were all mild in severity.

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.

Adult Crohn's Disease Clinical Studies

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

Pediatric Crohn's Disease Clinical Studies

HUMIRA has been studied in 192 pediatric patients with Crohn's disease in one double-blind study (Study PCD-I) and one open-label extension study. The safety profile for pediatric patients with Crohn's disease treated with HUMIRA was similar to the safety profile seen in adult patients with Crohn's disease.

During the 4 week open label induction phase of Study PCD-I, the most common adverse reactions occurring in the pediatric population treated with HUMIRA were injection site pain and injection site reaction (6% and 5%, respectively).

A total of 67% of children experienced an infection while receiving HUMIRA in Study PCD-I. These included upper respiratory tract infection and nasopharyngitis.

A total of 5% of children experienced a serious infection while receiving HUMIRA in Study PCD-I. These included viral infection, device related sepsis (catheter), gastroenteritis, H1N1 influenza, and disseminated histoplasmosis.

In Study PCD-I, allergic reactions were observed in 5% of children which were all non-serious and were primarily localized reactions.

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

General disorders and administration site conditions: Pyrexia

Hepato-biliary disorders: Liver failure, hepatitis

Immune system disorders: Sarcoidosis

Neoplasms benign, malignant and unspecified (including cysts and polyps): Merkel Cell Carcinoma (neuroendocrine carcinoma of the skin)

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 regarding the concomitant use of HUMIRA and other biologic products for the treatment of RA, PsA, AS, CD, UC, and Ps. Concomitant administration of HUMIRA with other biologic DMARDs (e.g., anakinra and abatacept) or other TNF blockers is not recommended based upon the possible increased risk for infections and other potential pharmacological interactions.

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

Risk Summary

Adequate and well controlled studies with HUMIRA have not been conducted in pregnant women. Adalimumab is an IgG1 monoclonal antibody and IgG1 is actively transferred across the placenta during the third trimester of pregnancy. Adalimumab serum levels were obtained from ten women treated with HUMIRA during pregnancy and eight newborn infants suggest active placental transfer of adalimumab. No fetal harm was observed in reproductive studies performed in cynomolgus monkeys. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Clinical Considerations

In general, monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

Human Data

In an independent clinical study conducted in ten pregnant women with inflammatory bowel disease treated with HUMIRA, adalimumab concentrations were measured in maternal blood as well as in cord (n=10) and infant blood (n=8) on the day of birth. The last dose of HUMIRA was given between 1 and 56 days prior to delivery. Adalimumab concentrations were 0.16-19.7 $\mu\text{g/mL}$ in cord blood, 4.28-17.7 $\mu\text{g/mL}$ in infant blood, and 0-16.1 $\mu\text{g/mL}$ in maternal blood. In all but one case, the cord blood level of adalimumab was higher than the maternal level, suggesting adalimumab actively crosses the placenta. In addition, one infant had levels at each of the following: 6 weeks (1.94 $\mu\text{g/mL}$), 7 weeks (1.31 $\mu\text{g/mL}$), 8 weeks (0.93 $\mu\text{g/mL}$), and 11 weeks (0.53 $\mu\text{g/mL}$), suggesting adalimumab can be detected in the serum of infants exposed in utero for at least 3 months from birth.

Animal Data

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.

8.3 Nursing Mothers

Limited data from published literature indicate that adalimumab is present in low levels in human milk and is not likely to be absorbed by a breastfed infant. However, no data is available on the absorption of adalimumab from breastmilk in newborn or preterm infants. Caution should be exercised when HUMIRA is administered to a nursing woman.

8.4 Pediatric Use

Safety and efficacy of HUMIRA in pediatric patients for uses other than polyarticular juvenile idiopathic arthritis (JIA) and pediatric Crohn's disease have not been established. Due to its inhibition of TNF α , HUMIRA administered during pregnancy could affect immune response in the *in utero*-exposed newborn and infant. Data from eight infants exposed to HUMIRA *in utero* suggest adalimumab crosses the placenta [see *Use in Specific Populations (8.1)*]. The clinical significance of elevated adalimumab levels in infants is unknown. The safety of administering live or live-attenuated vaccines in exposed infants is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

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

Juvenile Idiopathic Arthritis

In Study JIA-I, 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)*]. In Study JIA-II, the safety profile for patients 2 to <4 years of age was similar to the safety profile for patients 4 to 17 years of age with polyarticular JIA [see *Adverse Reactions (6.1)*]. HUMIRA has not been studied in patients with polyarticular JIA less than 2 years of age or in patients with a weight below 10 kg.

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

Pediatric Crohn's Disease

The safety and effectiveness of HUMIRA for reducing signs and symptoms and inducing and maintaining clinical remission have been established in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate. Use of HUMIRA in this age group is supported by evidence from adequate and well-controlled studies of HUMIRA in adults with additional data from a randomized, double-blind, 52-week clinical study of two dose levels of HUMIRA in 192 pediatric patients (6 to 17 years of age) with moderately to severely active Crohn's disease [see *Clinical Studies (14.6)*]. The safety and effectiveness of HUMIRA has not been established in pediatric patients with Crohn's disease less than 6 years of age.

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 patients and younger patients. The frequency of serious infection and malignancy among HUMIRA treated patients 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 overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

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), as a single-use, 1 mL prefilled glass syringe, or as a single-use institutional use vial. 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 40 mg/0.8 mL prefilled syringe, prefilled pen, or single-use institutional use vial delivers 0.8 mL (40 mg) of drug product. Each 0.8 mL of HUMIRA contains adalimumab 40 mg, citric acid monohydrate 1.04 mg, dibasic sodium phosphate dihydrate 1.22 mg, mannitol 9.6 mg, monobasic sodium phosphate dihydrate 0.69 mg, polysorbate 80 0.8 mg, sodium chloride 4.93 mg, sodium citrate 0.24 mg and Water for Injection, USP. Sodium hydroxide is added as necessary to adjust pH.

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

Each 10 mg/0.2 mL prefilled syringe delivers 0.2 mL (10 mg) of drug product. Each 0.2 mL of HUMIRA contains adalimumab 10 mg, citric acid monohydrate 0.26 mg, dibasic sodium phosphate dihydrate 0.31 mg, mannitol 2.4 mg, monobasic sodium phosphate dihydrate 0.17 mg,

polysorbate 80 0.2 mg, sodium chloride 1.23 mg, sodium citrate 0.06 mg and Water for Injection, USP. Sodium hydroxide is 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 IC_{50} of $1-2 \times 10^{-10}$ M).

12.2 Pharmacodynamics

After treatment with HUMIRA, a decrease in levels of acute phase reactants of inflammation (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and serum cytokines (IL-6) was observed compared to baseline in patients with rheumatoid arthritis. A decrease in CRP levels was also observed in patients with Crohn's disease 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 $4.7 \pm 1.6 \mu\text{g/mL}$ 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 $5 \mu\text{g/mL}$ and 8 to $9 \mu\text{g/mL}$, 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 Study JIA-I for patients with polyarticular JIA who were 4 to 17 years of age, the mean steady-state trough serum adalimumab concentrations for patients weighing <30 kg receiving 20 mg HUMIRA subcutaneously every other week as monotherapy or with concomitant MTX were 6.8 µg/mL and 10.9 µg/mL, respectively. The mean steady-state trough serum adalimumab concentrations for patients weighing ≥30 kg receiving 40 mg HUMIRA subcutaneously every other week as monotherapy or with concomitant MTX were 6.6 µg/mL and 8.1 µg/mL,

respectively. In Study JIA-II for patients with polyarticular JIA who were 2 to <4 years of age or 4 years of age and older weighing <15 kg, the mean steady-state trough serum adalimumab concentrations for patients receiving HUMIRA subcutaneously every other week as monotherapy or with concomitant MTX were 6.0 µg/mL and 7.9 µg/mL, respectively.

In pediatric subjects with CD weighing \geq 40 kg, the mean \pm SD serum adalimumab concentrations were 15.7 \pm 6.5 mcg/mL at Week 4 following subcutaneous doses of 160 mg at Week 0 and 80 mg at Week 2 and the mean \pm SD steady-state trough serum adalimumab concentrations were 10.5 \pm 6.0 mcg/mL at Week 52 following subcutaneous doses of 40 mg every other week. In pediatric subjects with CD weighing < 40 kg, the mean \pm SD serum adalimumab concentrations were 10.6 \pm 6.1 mcg/mL at Week 4 following subcutaneous doses of 80 mg at Week 0 and 40 mg at Week 2 and the mean \pm SD steady-state trough serum adalimumab concentrations were 6.9 \pm 3.6 mcg/mL at Week 52 following subcutaneous doses of 20 mg every other week.

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 \geq 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)

| Response | Study RA-II Monotherapy (26 weeks) | | | Study RA-III Methotrexate Combination (24 and 52 weeks) | |
|--------------|--|-------------------------------------|------------------------|---|---|
| | Placebo | HUMIRA 40 mg every other week | HUMIRA 40 mg weekly | Placebo/MTX | HUMIRA/MTX 40 mg every other week |
| | N=110 | N=113 | N=103 | N=200 | 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.

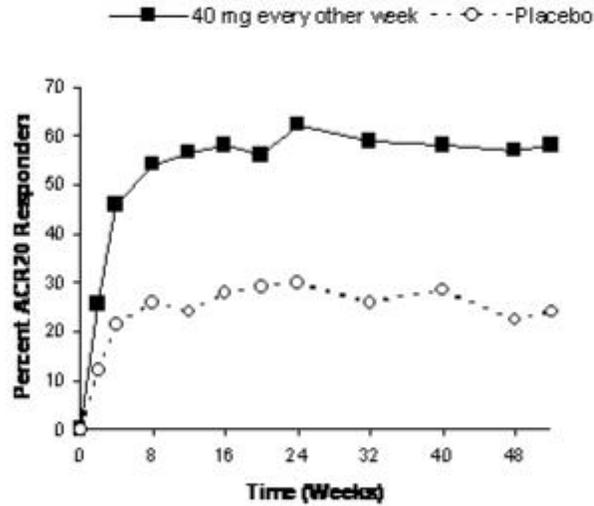
Table 3. Components of ACR Response in Studies RA-II and RA-III

| 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 | | | |
| Week 52 | 63% | 54% | 73% |
| Week 104 | 56% | 49% | 69% |
| ACR50 | | | |
| Week 52 | 46% | 41% | 62% |
| Week 104 | 43% | 37% | 59% |
| ACR70 | | | |
| Week 52 | 27% | 26% | 46% |
| Week 104 | 28% | 28% | 47% |
| Major Clinical Response ^a | 28% | 25% | 49% |
| ^a Major clinical response is defined as achieving an ACR70 response for a continuous six month period | | | |
| ^b $p < 0.05$, HUMIRA/MTX vs. MTX for ACR 20 | | | |

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

At Week 52, all individual components of the ACR response criteria for Study 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 Interval*) | P-value** |
|--|-------------|---|--|-----------|
| Total Sharp score | 2.7 | 0.1 | 2.6 (1.4, 3.8) | <0.001 |
| Erosion score | 1.6 | 0.0 | 1.6 (0.9, 2.2) | <0.001 |
| JSN score | 1.0 | 0.1 | 0.9 (0.3, 1.4) | 0.002 |
| *95% confidence intervals for the differences in change scores between MTX and HUMIRA. | | | | |
| **Based on rank analysis | | | | |

In the open-label extension of Study 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 was assessed in two studies (Studies JIA-I and JIA-II) in patients with active polyarticular juvenile idiopathic arthritis (JIA).

Study JIA-I

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

Study JIA-I 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.

Study JIA-II

HUMIRA was assessed in an open-label, multicenter study in 32 patients who were 2 to <4 years of age or 4 years of age and older weighing <15 kg with moderately to severely active polyarticular JIA. Most patients (97%) received at least 24 weeks of HUMIRA treatment dosed 24 mg/m² up to a maximum of 20 mg every other week as a single SC injection up to a maximum of 120 weeks duration. During the study, most patients used concomitant MTX, with fewer reporting use of corticosteroids or NSAIDs. The primary objective of the study was evaluation of safety [*see Adverse Reactions (6.1)*].

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 | | |
| Week 12 | 14% | 58% |
| Week 24 | 15% | 57% |
| ACR50 | | |
| Week 12 | 4% | 36% |
| Week 24 | 6% | 39% |
| ACR70 | | |
| Week 12 | 1% | 20% |
| Week 24 | 1% | 23% |
| * p<0.001 for all comparisons between HUMIRA and placebo | | |

Table 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.

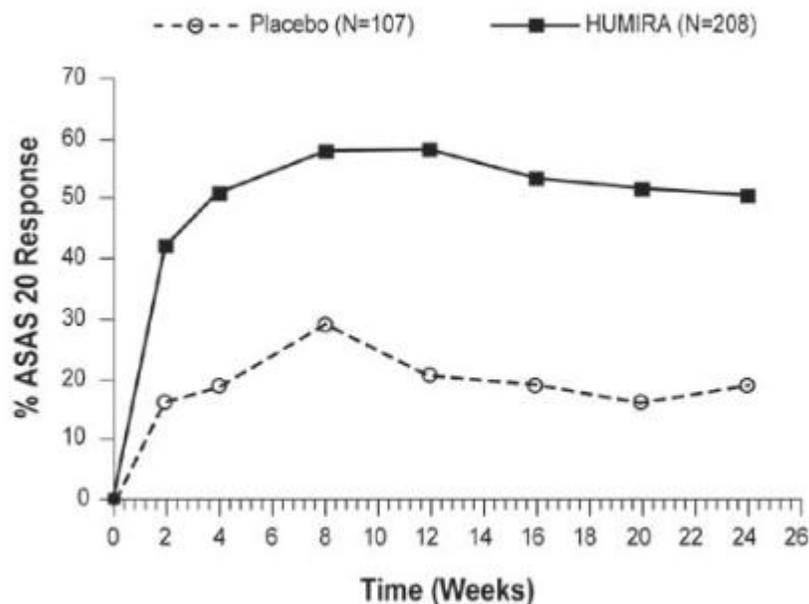
14.4 Ankylosing Spondylitis

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 Adult 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) \geq 220 and \leq 450) in randomized, double-blind, placebo-controlled studies. Concomitant stable doses of aminosaliculates, 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 Pediatric Crohn's Disease

A randomized, double-blind, 52-week clinical study of 2 dose levels of HUMIRA (Study PCD-I) was conducted in 192 pediatric patients (6 to 17 years of age) with moderately to severely active Crohn's disease (defined as Pediatric Crohn's Disease Activity Index (PCDAI) score > 30).² Enrolled patients had over the previous two year period an inadequate response to corticosteroids or an immunomodulator (i.e., azathioprine, 6-mercaptopurine, or methotrexate). Patients who had previously received a TNF blocker were allowed to enroll if they had previously had loss of response or intolerance to that TNF blocker.

Patients received open-label induction therapy at a dose based on their body weight (≥ 40 kg and <40 kg). Patients weighing ≥ 40 kg received 160 mg (at Week 0) and 80 mg (at Week 2). Patients weighing <40 kg received 80 mg (at Week 0) and 40 mg (at Week 2). At Week 4, patients within each body weight category (≥ 40 kg and <40 kg) were randomized 1:1 to one of two maintenance dose regimens (high dose and low dose). The high dose was 40 mg every other week for patients weighing ≥ 40 kg and 20 mg every other week for patients weighing <40 kg. The low dose was 20 mg every other week for patients weighing ≥ 40 kg and 10 mg every other week for patients weighing <40 kg.

Concomitant stable dosages of corticosteroids (prednisone dosage ≤ 40 mg/day or equivalent) and immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate) were permitted throughout the study.

At Week 12, patients who experienced a disease flare (increase in PCDAI of ≥ 15 from Week 4 and absolute PCDAI > 30) or who were non-responders (did not achieve a decrease in the PCDAI of ≥ 15 from baseline for 2 consecutive visits at least 2 weeks apart) were allowed to dose-escalate (i.e., switch from blinded every other week dosing to blinded every week dosing); patients who dose-escalated were considered treatment failures.

At baseline, 38% of patients were receiving corticosteroids, and 62% of patients were receiving an immunomodulator. Forty-four percent (44%) of patients had previously lost response or were intolerant to a TNF blocker. The median baseline PCDAI score was 40.

Of the 192 patients total, 188 patients completed the 4 week induction period, 152 patients completed 26 weeks of treatment, and 124 patients completed 52 weeks of treatment. Fifty-one percent (51%) (48/95) of patients in the low maintenance dose group dose-escalated, and 38% (35/93) of patients in the high maintenance dose group dose-escalated.

At Week 4, 28% (52/188) of patients were in clinical remission (defined as PCDAI \leq 10).

The proportions of patients in clinical remission (defined as PCDAI \leq 10) and clinical response (defined as reduction in PCDAI of at least 15 points from baseline) were assessed at Weeks 26 and 52.

At both Weeks 26 and 52, the proportion of patients in clinical remission and clinical response was numerically higher in the high dose group compared to the low dose group (Table 13). The recommended maintenance regimen is 20 mg every other week for patients weighing < 40 kg and 40 mg every other week for patients weighing \geq 40 kg. Every week dosing is not the recommended maintenance dosing regimen [see *Dosage and Administration* (2.4)].

Table 13. Clinical Remission and Clinical Response in Study PCD-I

| | Low Maintenance Dose[†] (20 or 10 mg every other week) N = 95 | High Maintenance Dose[#] (40 or 20 mg every other week) N = 93 |
|---|---|--|
| Week 26 | | |
| Clinical Remission [‡] | 28% | 39% |
| Clinical Response [§] | 48% | 59% |
| Week 52 | | |
| Clinical Remission [‡] | 23% | 33% |
| Clinical Response [§] | 28% | 42% |
| [†] The low maintenance dose was 20 mg every other week for patients weighing \geq 40 kg and 10 mg every other week for patients weighing < 40 kg. [#] The high maintenance dose was 40 mg every other week for patients weighing \geq 40 kg and 20 mg every other week for patients weighing < 40 kg. [‡] Clinical remission defined as PCDAI \leq 10. [§] Clinical response defined as reduction in PCDAI of at least 15 points from baseline. | | |

14.7 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 14).

| Table 14. 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.

14.8 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 15 and 16).

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

| | HUMIRA 40 mg every other week | Placebo |
|---|-------------------------------|---------|
| | N = 814 | 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 16. Efficacy Results at 16 Weeks in Study Ps-II Number of Patients (%)

| | HUMIRA 40 mg every other week | Placebo |
|---|-------------------------------|---------|
| | N = 99 | 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.
2. Hyams JS, Ferry GD, Mandel FS, et al. Development and validation of a pediatric Crohn’s disease activity index. *J Pediatr Gastroenterol Nutr.* 1991;12:439-447.

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 Prefilled Syringe - Pediatric Crohn's Disease Starter Package (6 count)**
HUMIRA is dispensed in a carton containing 6 alcohol preps and 6 dose trays (Pediatric Starter Package). 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 0074-3799-06.
- **HUMIRA Prefilled Syringe - Pediatric Crohn's Disease Starter Package (3 count)**
HUMIRA is dispensed in a carton containing 4 alcohol preps and 3 dose trays (Pediatric Starter Package). 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 0074-3799-03.
- **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.
- **Prefilled Syringe Carton - 20 mg**
HUMIRA is supplied 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.
- **Prefilled Syringe Carton - 10 mg**
HUMIRA is supplied 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 10 mg/0.2 mL of HUMIRA. The NDC number is 0074-6347-02.

- **Single-Use 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. Store in original carton until time of administration to protect from light.

If needed, for example when traveling, HUMIRA may be stored at room temperature up to a maximum of 77°F (25°C) for a period of up to 14 days, with protection from light. HUMIRA should be discarded if not used within the 14-day period. Record the date when HUMIRA is first removed from the refrigerator in the spaces provided on the carton and dose tray.

Do not store HUMIRA in extreme heat or cold.

17 PATIENT COUNSELING INFORMATION

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

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.

Instructions 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.

US License Number 1889

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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 2 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.
 - **moderate to severe Crohn's disease (CD) in children 6 years and older** 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 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.
- 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 over-the-counter 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 the refrigerator between 36°F to 46°F (2°C to 8°C). Store HUMIRA in the original carton until use to protect it from light.
- **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 HUMIRA after the expiration date.
- If needed, for example when you are traveling, you may also store HUMIRA at room temperature up to 77°F (25°C) for up to **14** days. Store HUMIRA in the original carton until use to protect it from light.
- Throw away HUMIRA if it has been kept at room temperature and not been used within **14** days.
- Record the date you first remove HUMIRA from the refrigerator in the spaces provided on the carton and dose tray.
- Do not store HUMIRA in extreme heat or cold.
- 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 health 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: citric acid monohydrate, dibasic sodium phosphate dihydrate, mannitol, monobasic sodium phosphate dihydrate, polysorbate 80, sodium chloride, sodium citrate 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.

Manufactured by:

AbbVie Inc.

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

US License Number 1889

03-XXXX

Revised: 12/2014

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 and have read and understand this Instructions for Use. 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. It is also important to talk to your doctor to be sure you understand your HUMIRA dosing instructions. To help you remember when to inject HUMIRA, you can mark your calendar ahead of time. 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”**.

Gather the Supplies for Your Injection

- You will need the following supplies for each injection of HUMIRA.

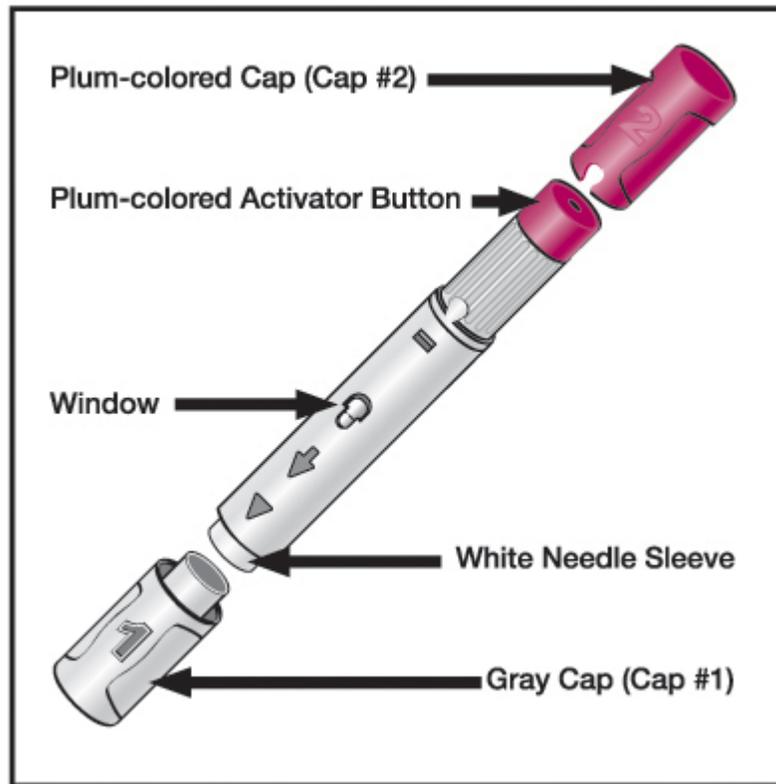
Find a clean, flat surface to place the supplies on.

- 1 alcohol swab
- 1 cotton ball or gauze pad (not included in your HUMIRA carton)
- 1 HUMIRA Pen (See Figure A)
- FDA-cleared sharps disposal container for HUMIRA Pen disposal (not included in your HUMIRA carton)

If more comfortable, take your HUMIRA Pen out of the refrigerator **15 to 30 minutes** before injecting to allow the liquid to reach room temperature. **Do not** remove the gray or plum-colored caps while allowing it to reach room temperature. **Do not** warm HUMIRA in any other way (for example, **do not** warm it in a microwave or in hot water).

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



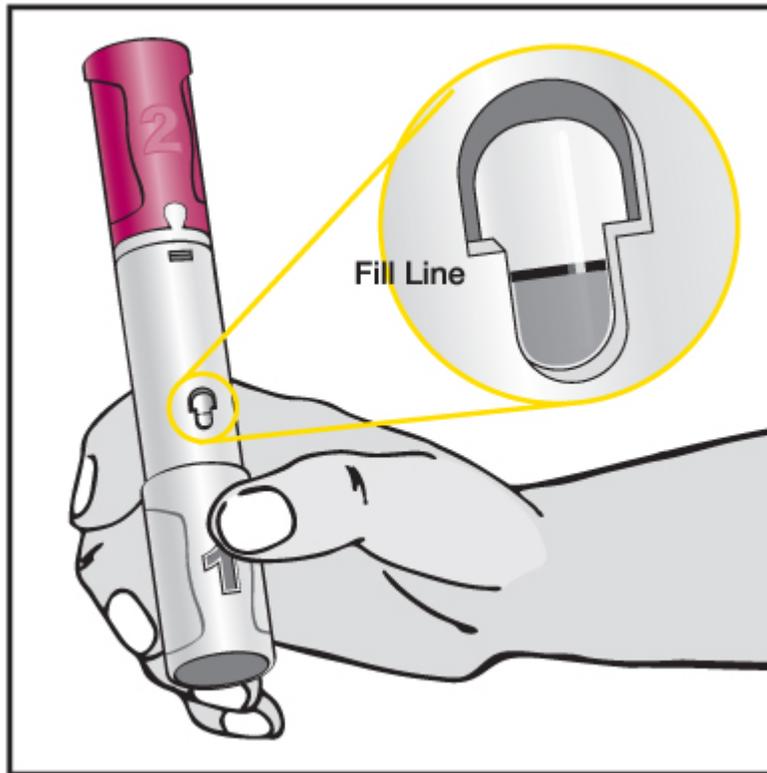
Check the carton, dose tray, and HUMIRA Pen.

1. Make sure the name HUMIRA appears on the carton, dose tray, and HUMIRA Pen label.
2. **Do not use** and **do 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.
 - HUMIRA has been kept at room temperature for longer than **14** days or HUMIRA has been stored above 77°F (25°C).

See the **“How should I store HUMIRA?”** section at the end of this 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.

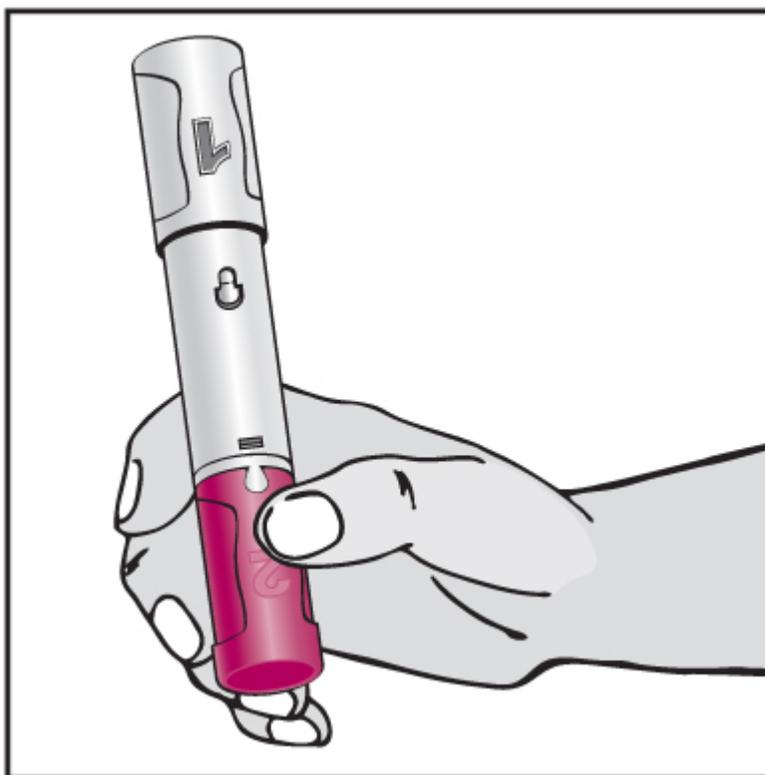
Figure B



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.

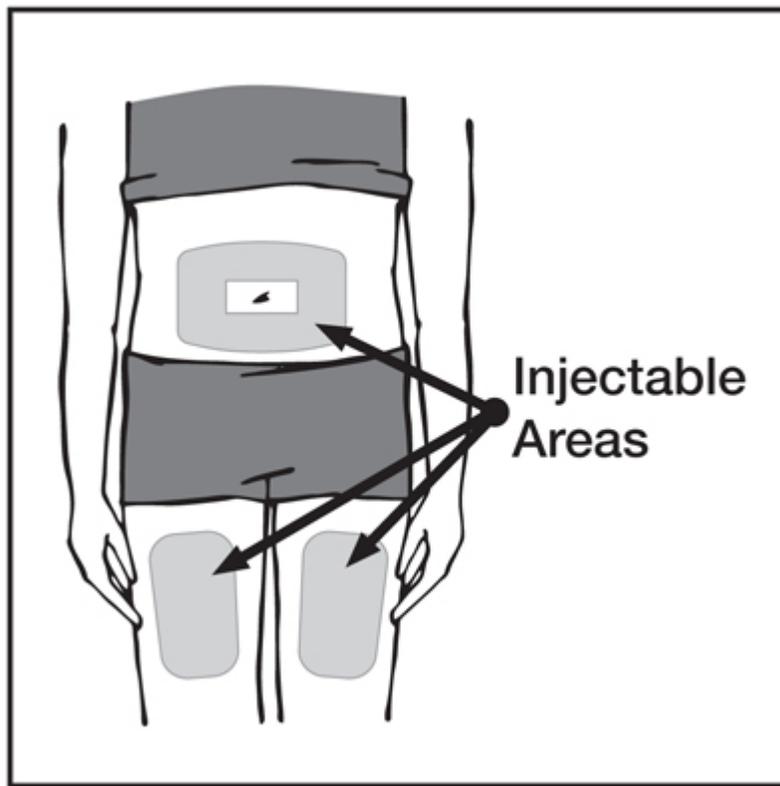
Figure C



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

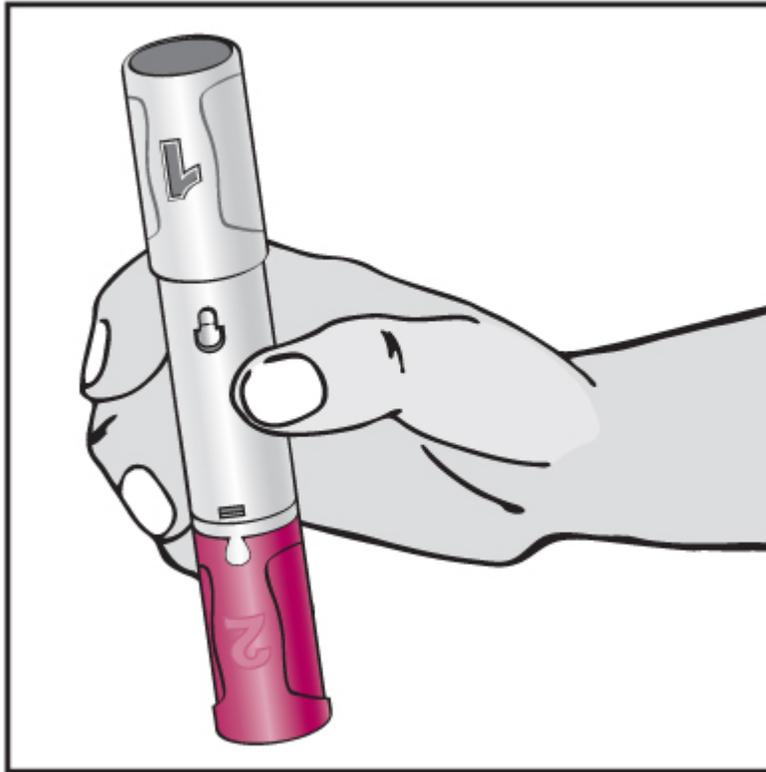
10. Wipe the injection site with an alcohol prep (swab) using a circular motion.
 - **Do not** touch this area again before giving the injection. Allow the skin to dry before injecting. **Do not** fan or blow on the clean area.

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.

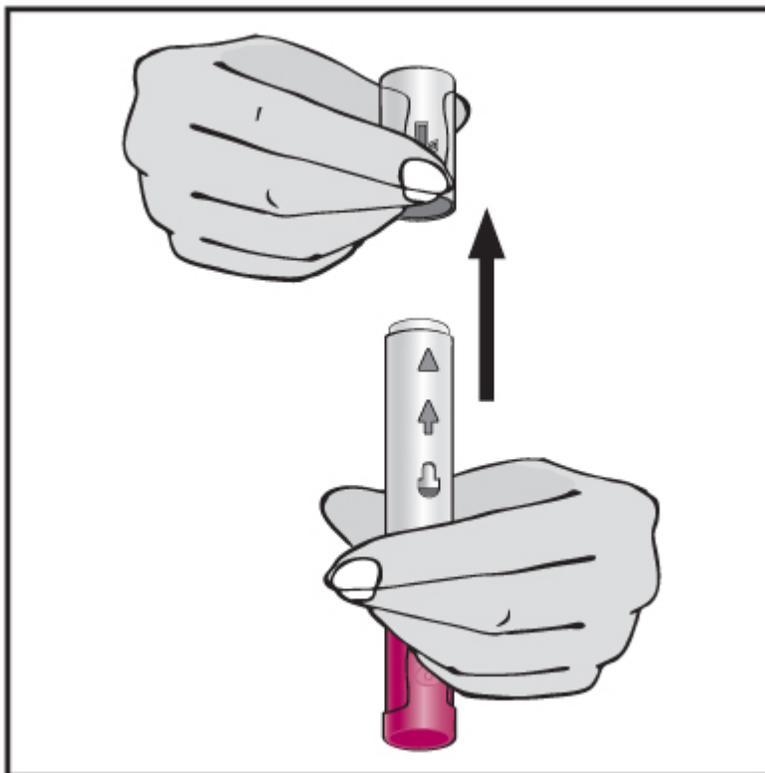
Figure E



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.

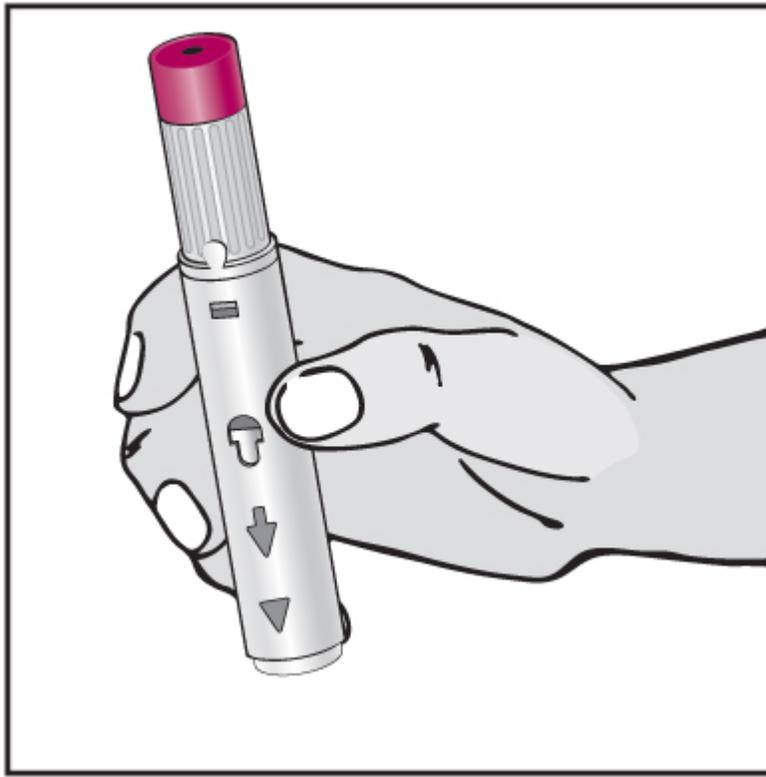
15. Remove the plum-colored cap (Cap # 2) from the bottom of the Pen by pulling it straight off (do not twist the cap). The Pen is now activated. Throw away the plum-colored cap.

- 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:

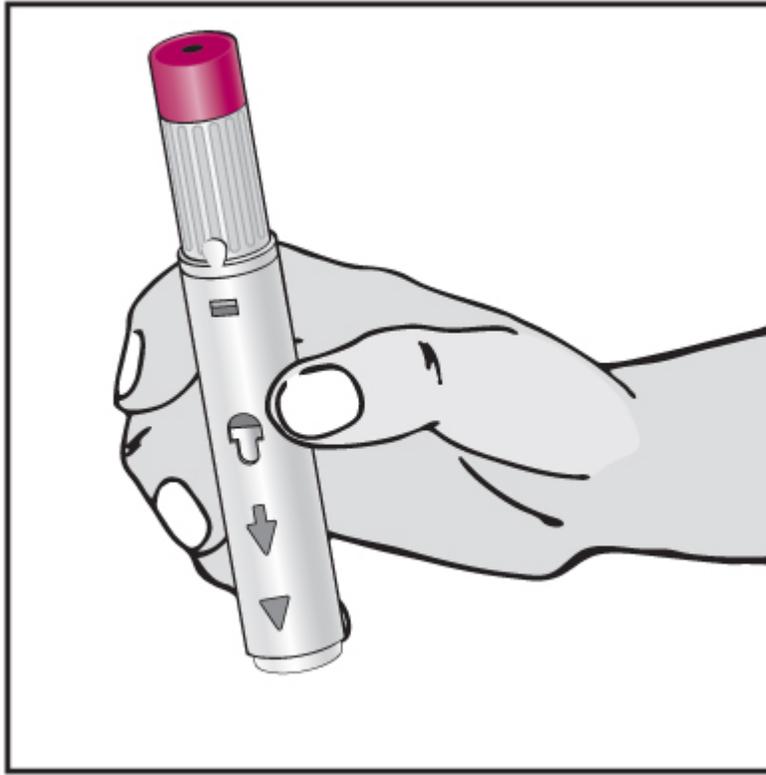
- Turn the Pen so the plum-colored activator button is pointed up. See Figure G.

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:

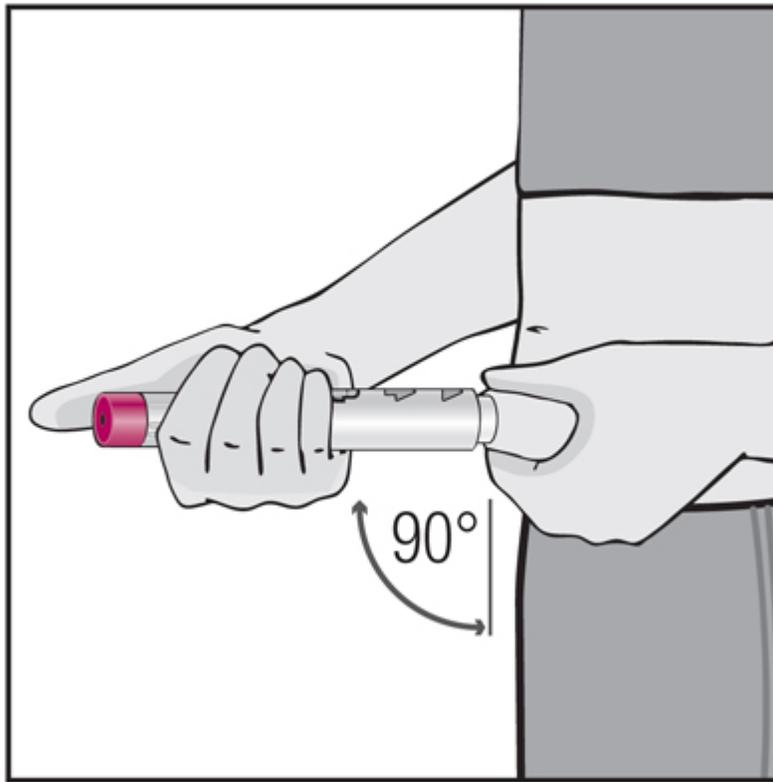
- Gently squeeze the area of the cleaned skin and hold it firmly. See Figure I. You will inject into this raised area of skin.

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.

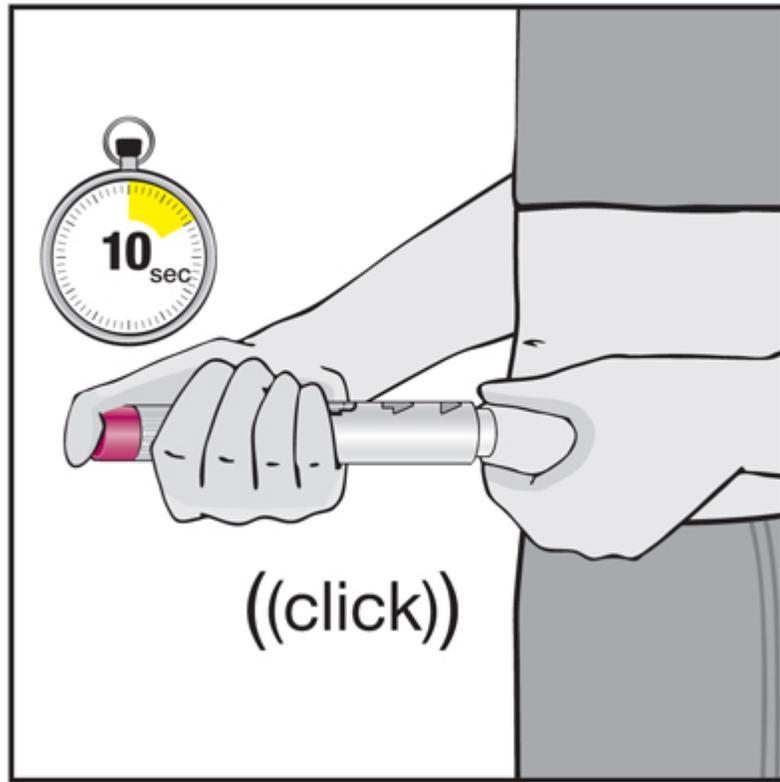
Figure J



18. Inject HUMIRA

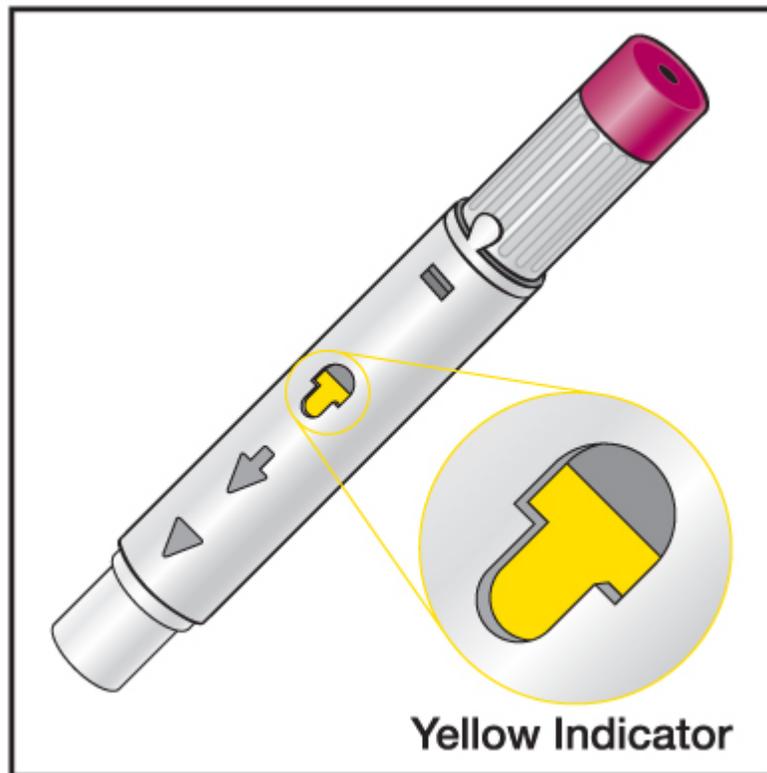
- With your index finger or your thumb, press the plum-colored activator button to begin the injection. Try not to cover the window. See Figure K.

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.

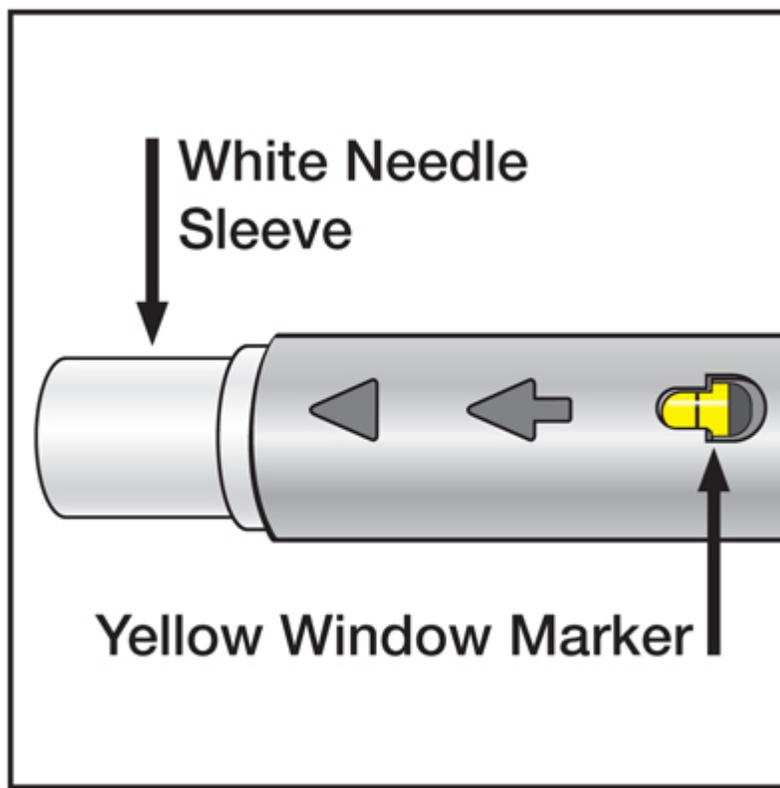
Figure L



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.

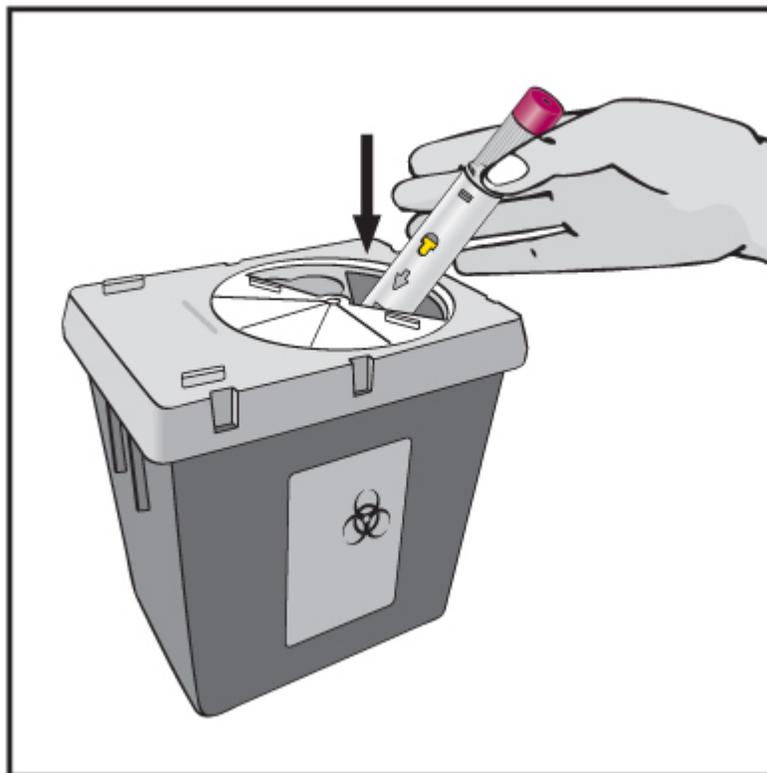
20. Dispose of your used HUMIRA Pen. See the section “**How should I dispose of the used HUMIRA Pen?**”

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.**

How should I store HUMIRA?

- Store HUMIRA in the refrigerator between 36°F to 46°F (2°C to 8°C). Store HUMIRA in the original carton until use to protect it from light.
- **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 or Pen. **Do not** use HUMIRA after the expiration date.
- If needed, for example when you are traveling, you may also store HUMIRA at room temperature up to 77°F (25°C) for up to **14** days. Store HUMIRA in the original carton until use to protect it from light.
- Throw away HUMIRA if it has been kept at room temperature and not been used within **14** days.
- Record the date you first remove HUMIRA from the refrigerator in the spaces provided on the carton and dose tray.
- Do not store HUMIRA in extreme heat or cold.
- 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.

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

Manufactured by:

AbbVie Inc.

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

US License Number 1889

03-XXXX

Revised: 12/2014

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 and have read and understand this Instructions for Use. 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. It is also important to talk to your doctor to be sure you understand your HUMIRA dosing instructions. To help you remember

when to inject HUMIRA, you can mark your calendar ahead of time. Call your healthcare provider if you or your caregiver has any questions about the right way to inject HUMIRA.

Gather the Supplies for Your Injection

- You will need the following supplies for each injection of HUMIRA.

Find a clean, flat surface to place the supplies on.

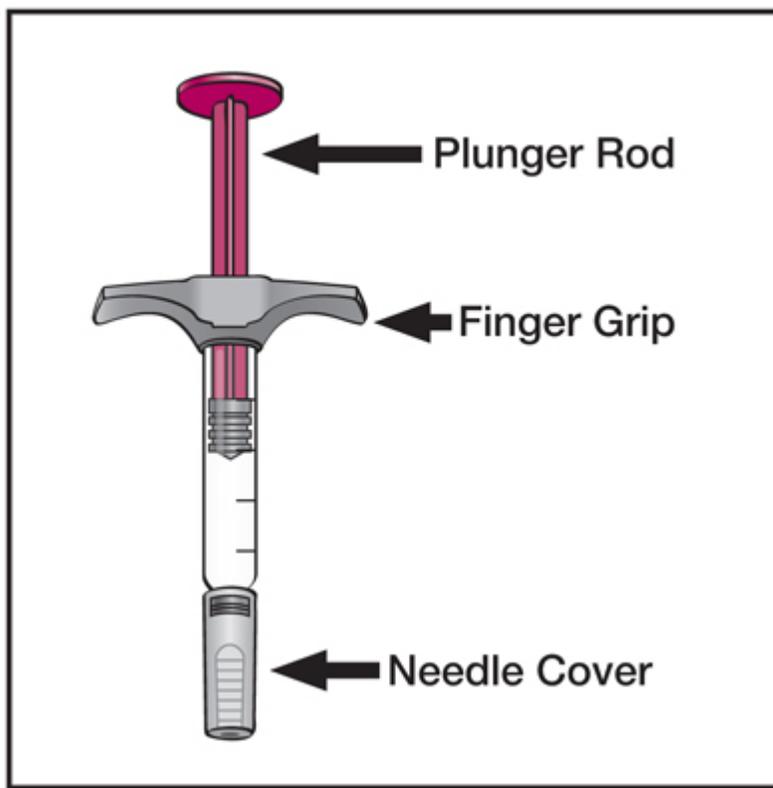
- 1 alcohol swab
- 1 cotton ball or gauze pad (not included in your HUMIRA carton)
- 1 HUMIRA prefilled syringe (See Figure A)
- FDA-cleared sharps disposal container for HUMIRA prefilled syringe disposal (not included in your HUMIRA carton)

If more comfortable, take your HUMIRA prefilled syringe out of the refrigerator **15 to 30 minutes** before injecting to allow the liquid to reach room temperature. **Do not** remove the needle cover while allowing it to reach room temperature. **Do not** warm HUMIRA in any other way (for example, **do not** warm it in a microwave or in hot water).

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 **do call** your doctor or pharmacist if:
 - the seals on top or 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.
 - HUMIRA has been kept at room temperature for longer than **14** days or HUMIRA has been stored above 77°F (25°C).
 - the liquid in the prefilled syringe is cloudy, discolored or has flakes or particles in it. Make sure the liquid is clear and colorless.

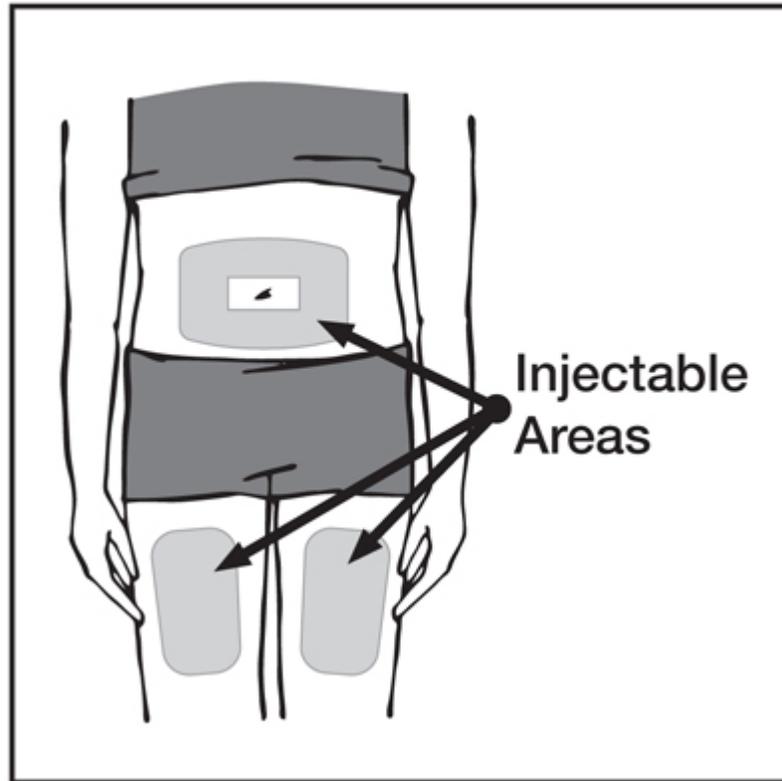
See the **“How should I store HUMIRA?”** section at the end of this Instructions for Use.

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

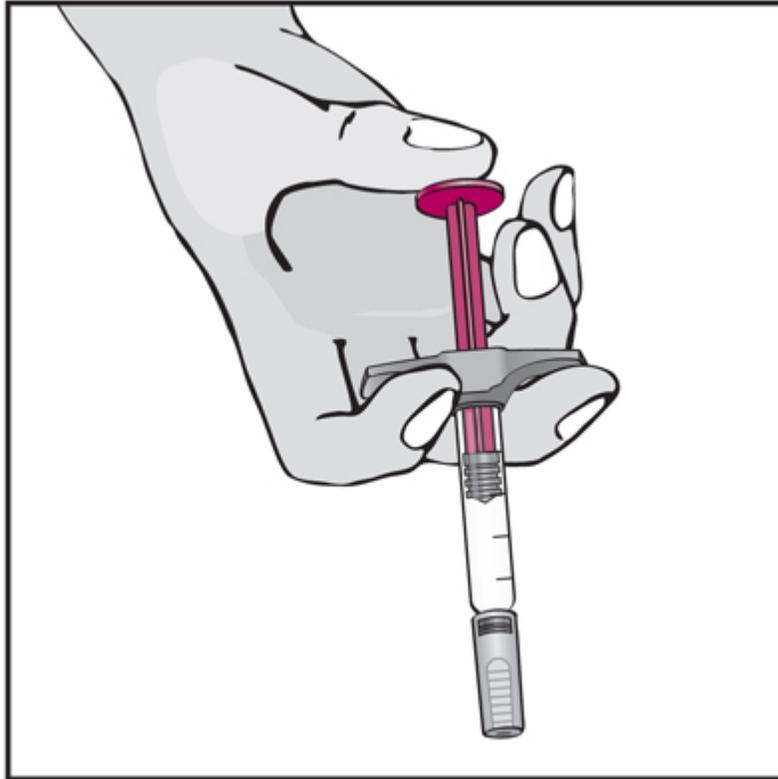
5. Wipe the injection site with an alcohol prep (swab) using a circular motion.
6. Do **not** touch this area again before giving the injection. Allow the skin to dry before injecting. Do not fan or blow on the clean area.

Prepare the Syringe and Needle

7. Check the fluid level in the syringe:

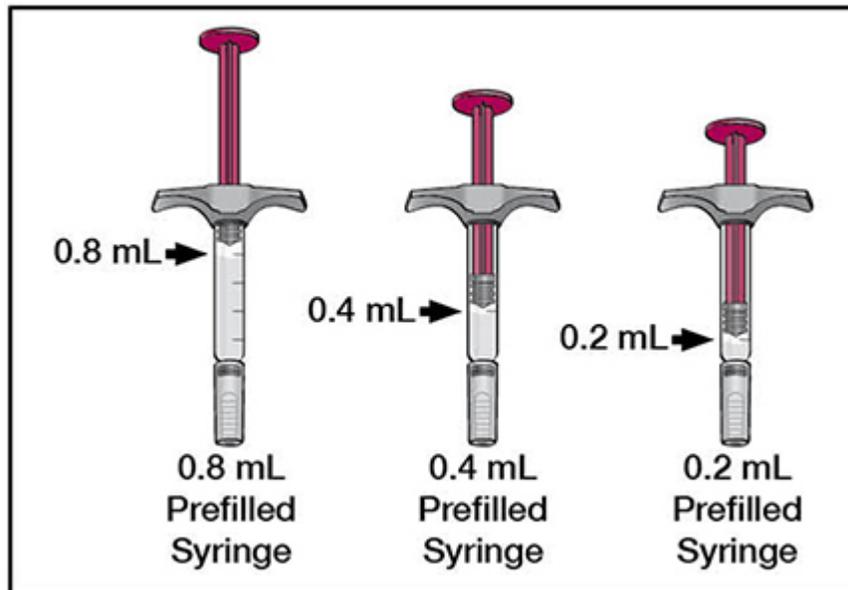
- Always hold the prefilled syringe by the body of the syringe. Hold the syringe with the covered needle pointing down. See Figure C.

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. See Figure D.
 - 0.4 mL line for the 20 mg prefilled syringe. See Figure D.
 - 0.2 mL line for the 10 mg prefilled syringe. See Figure D.

Figure D

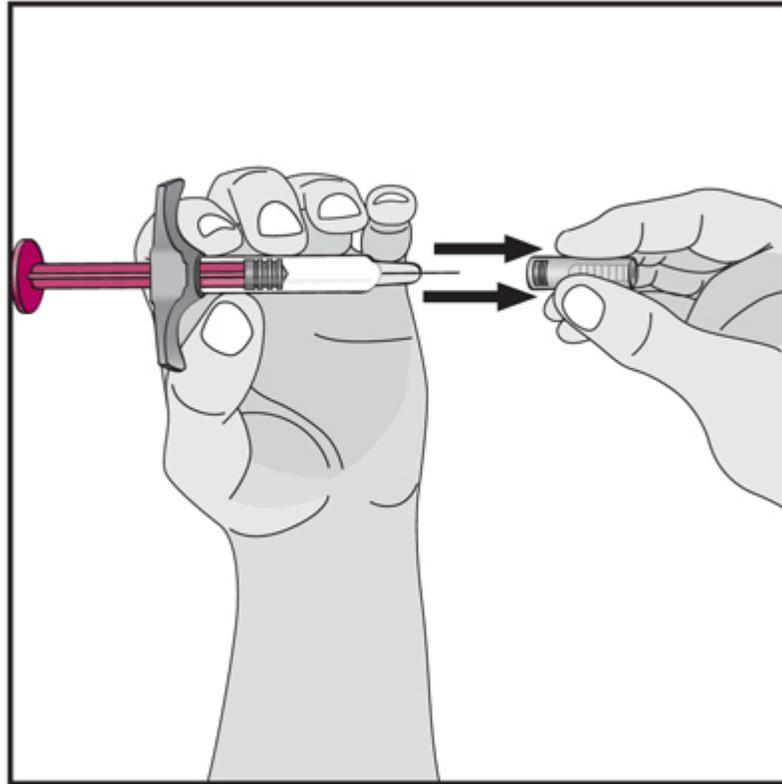


8. The top of the liquid may be curved. If the syringe does not have the correct amount of liquid, **do not use that syringe**. Call your pharmacist.

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.

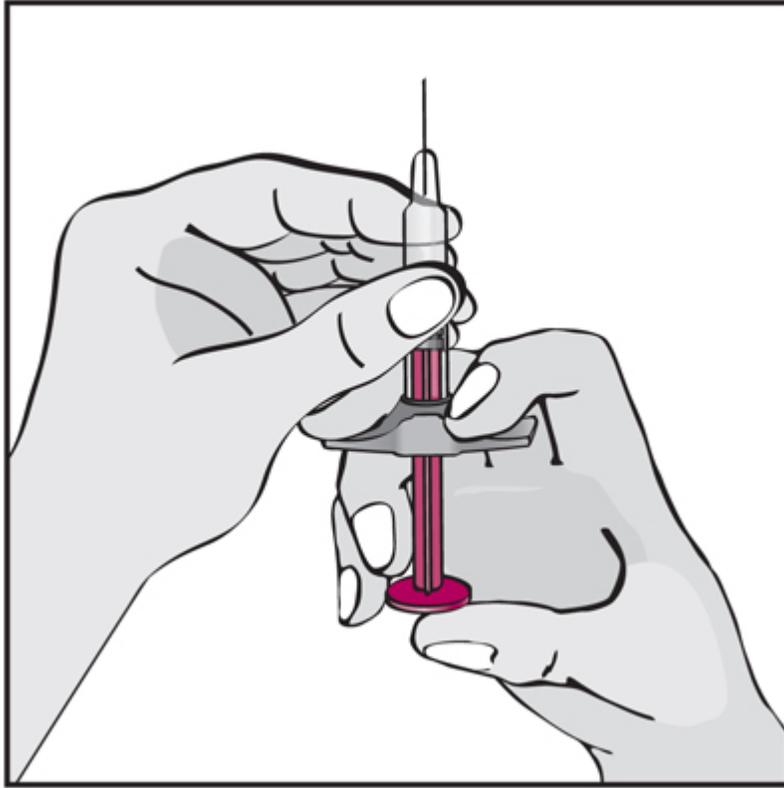
Figure E



- 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



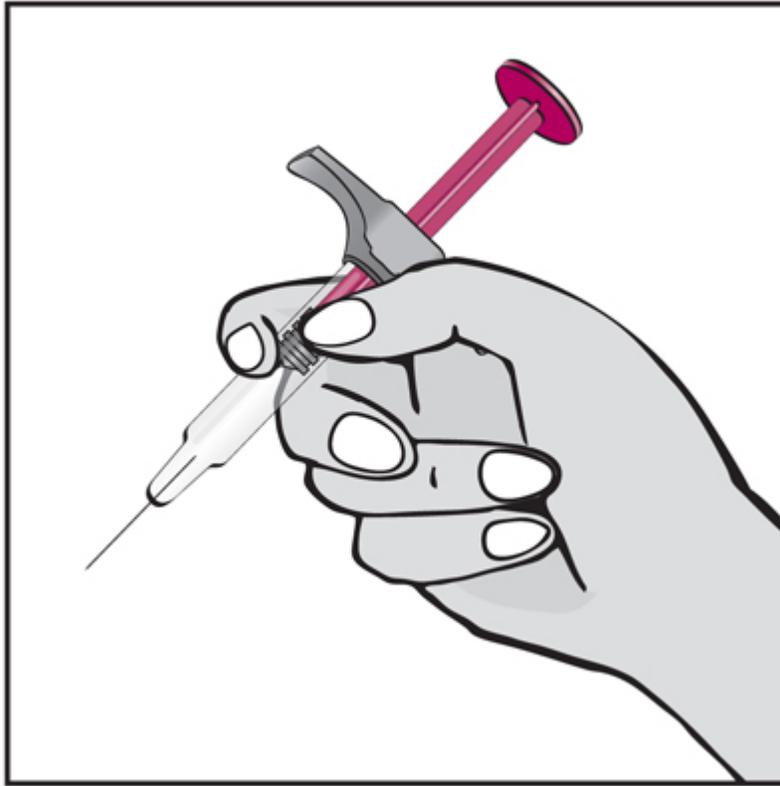
- You may see a drop of liquid at the end of the needle. This is normal.

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.

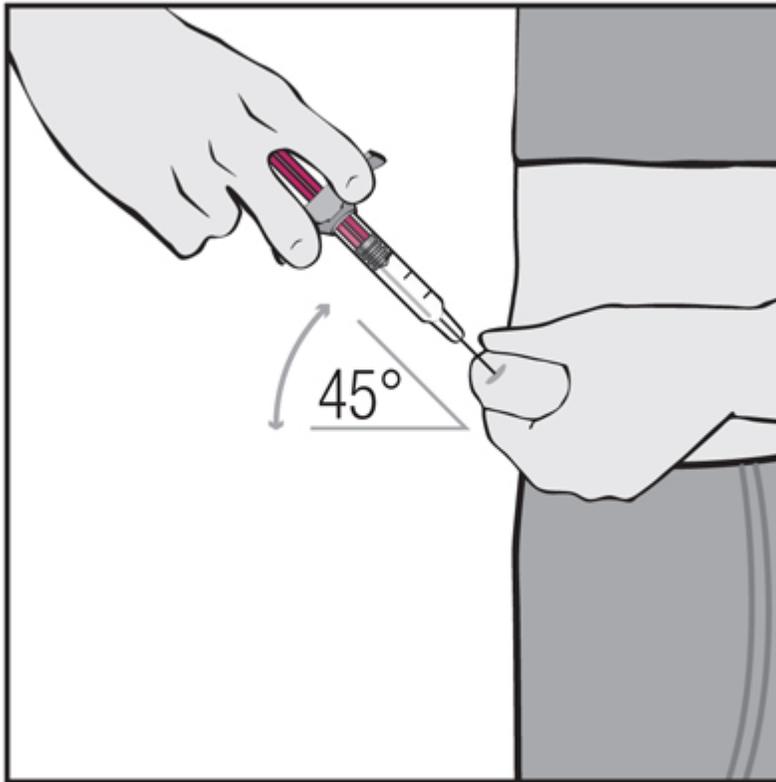
Figure H



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

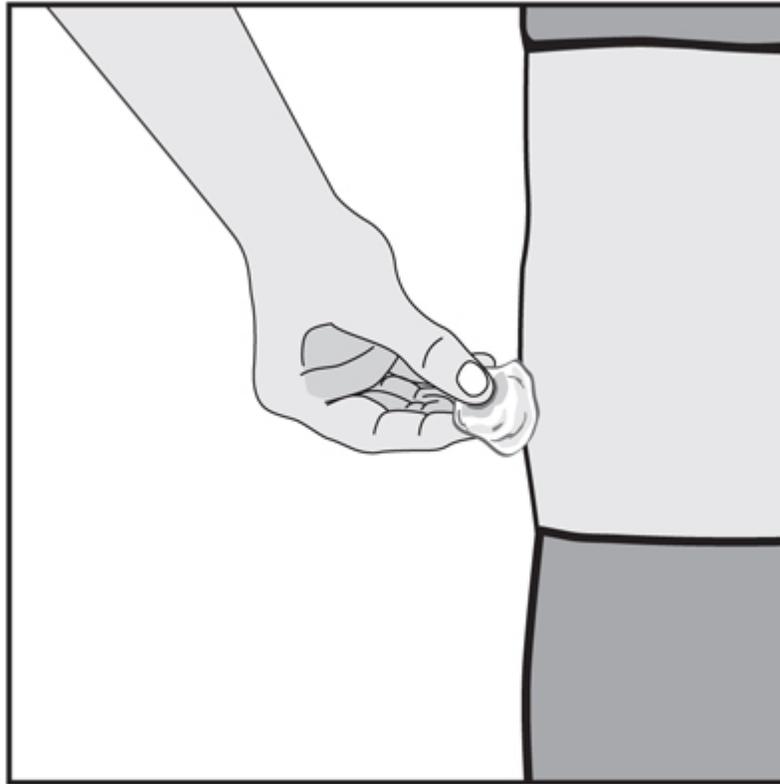


- After the needle is in, let go of the skin. Pull back gently on the plunger.

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.

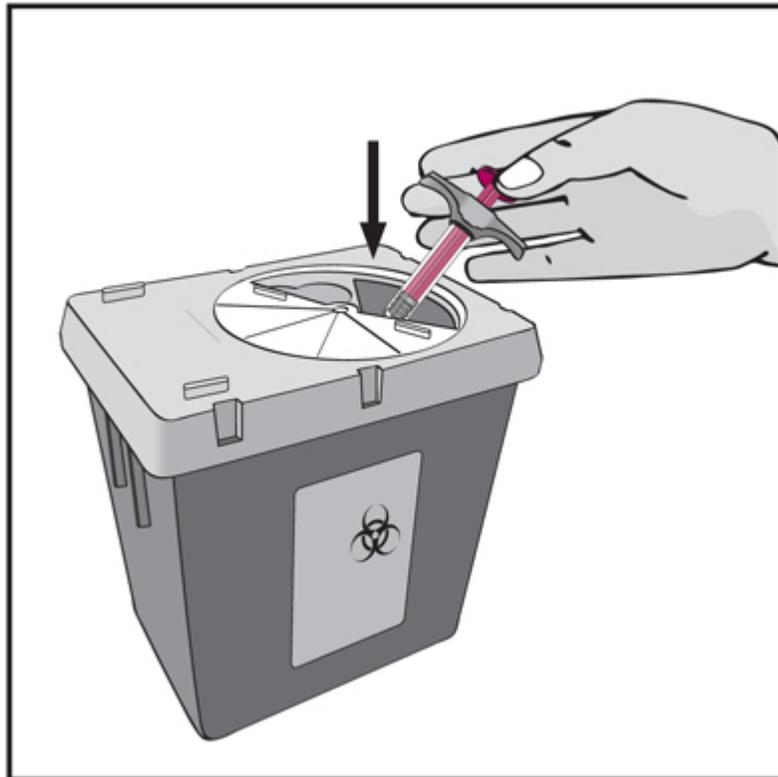
13. Throw away the used prefilled syringe and needle. See **“How should I dispose of used prefilled syringes and needles?”**

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.**

How should I store HUMIRA?

- Store HUMIRA in the refrigerator between 36°F to 46°F (2°C to 8°C). Store HUMIRA in the original carton until use to protect it from light.
- **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 or prefilled syringe. **Do not** use HUMIRA after the expiration date.
- If needed, for example when you are traveling, you may also store HUMIRA at room temperature up to 77°F (25°C) for up to **14** days. Store HUMIRA in the original carton until use to protect it from light.
- Throw away HUMIRA if it has been kept at room temperature and not been used within **14** days.
- Record the date you first remove HUMIRA from the refrigerator in the spaces provided on the carton and dose tray.
- Do not store HUMIRA in extreme heat or cold.
- 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.

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

Manufactured by:

AbbVie Inc.

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

US License Number 1889

03-XXXX

Revised: 12/2014

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
BLA 125057/S-280

MEDICAL REVIEW(S)



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY PRODUCTS
10903 New Hampshire Avenue; Building 22
Silver Spring MD 20993-0002**

Medical Officer Review

| | |
|-----------------------------|---------------------------------|
| BLA: | 125057/280 |
| Drug name: | Humira® (Adalimumab) |
| Applicant: | Abbvie |
| Indication: | Rheumatoid Arthritis |
| Type of Submissions: | Prior Approval Supplement (CMC) |
| Date of Submission: | June 26, 2014 |
| Date of Receipt: | June 26, 2014 |
| eCTD#: | 304 |
| SD: | 4701 |
| Review Date: | December 24, 2014 |
| Reviewer: | Janet W. Maynard, M.D. |

1. Introduction and Executive Summary

This review evaluates proposed modifications made by the Applicant to change the Humira storage instructions to allow for a limited room temperature storage option for the Humira prefilled syringes, Humira pen (autoinjector), and Humira institutional vial presentations. Specifically, the proposed label changes will allow storage of Humira up to 77°F (25°C) for a single instance of up to 14 days. The changes would apply to all five of the currently approved Humira presentations (10mg prefilled syringe, 20mg prefilled syringe, 40mg prefilled syringe, 40mg pen, and 40mg institutional vial). According to the Applicant, the benefit of a limited room temperature storage option is one of convenience, affording patients improved flexibility in special situations, such as when traveling or otherwise absent from home, where refrigeration is either not practical or possible.

The Applicant initially submitted the supplement on December 29, 2011, and received a complete response on April 27, 2012. The primary concern was that the product would not be stored in the appropriate temperature range.

Type C meeting written responses were issued on November 26, 2013. The Agency noted that the stability data and updated labeling should be sufficient to support the proposed room temperature storage condition. The Agency did not feel additional data, such as human factors data or label comprehension data, were needed.

The Applicant submitted revised labeling, including changes made to the prescribing information, Medication Guide, Pen instructions for use, and prefilled syringe instructions for use. In addition, statements regarding unrefrigerated expiration of Humira are included on the dose tray print mats, which the Applicant notes was recommended by the Agency on May 16, 2012.

This prior approval supplement has been reviewed by the Office of Biological Products (OBP), the Division of Medication Error Prevention and Analysis (DMEPA), the patient labeling team, and the Center for Devices and Radiological Health (CDRH). The primary data to support this supplement comes from stability data with associated updated labeling. All reviewing disciplines felt the data were adequate to support approval. Thus, the overall recommendation is approval of this supplement.

1.1 Recommendations for Regulatory Action

The recommendation is for approval of this supplement.

2. Regulatory History

Humira is a human-derived monoclonal antibody to TNF α that was initially approved on 12/31/02 for the treatment of rheumatoid arthritis (RA). It was subsequently approved for psoriatic arthritis (11/9/06), ankylosing spondylitis (11/9/06), Crohn's disease (2/27/02), polyarticular juvenile idiopathic arthritis for children (2/21/08), and plaque psoriasis (1/18/08). Currently, there are five dosage forms and strength of Humira: 40mg

prefilled pen, 40mg prefilled syringe, 20mg prefilled syringe, 10mg prefilled syringe, and 40mg single-use glass vial.

The Applicant initially submitted Prior Approval Supplement 125057/280 on December 29, 2011, and received a complete response on April 27, 2012. The deficiencies noted in the complete response letter were:

1. Storage of biologic products under controlled room temperature conditions is unusual and there is great concern over the ability of patients to consistently maintain the product within the validated storage temperature ($\leq 25^{\circ}\text{C}$). Provide all available information with regard to how controlled room temperature will be maintained and monitored by the patient such as a mechanism to monitor whether storage conditions have exceeded the recommended temperature limit (e.g. a colorimetric temperature indicator). Include information/data which adequately support that control over the controlled room temperature by the patient is sufficient to assure product will be stored within its validated storage temperature.
2. You have not included an updated medication guide that incorporates your proposed changes to the recommended storage conditions consistent with changes noted in the package insert and patient instructions.
3. Please provide a risk assessment for temperature excursions beyond controlled room temperature while drug product is under patient control.

Type C meeting written responses were issued on November 26, 2013. The Agency noted that the stability data and updated labeling should be sufficient to support the proposed room temperature storage condition. The Agency did not feel additional data, such as human factors data or label comprehension data, were needed.

The Applicant resubmitted BLA 125057/280 on June 26, 2014. Consistent with the Agency's recommendations in written responses dated November 26, 2013, the Applicant submitted stability data and updated labeling to support the proposed limited room temperature storage option.

3. Overview of Changes Proposed in this Prior Approval Supplement

The purpose of this labeling supplement is to allow a limited room temperature storage option for the Humira prefilled syringes, Humira Pen, and Humira institutional vial presentations. The changes would apply to all currently approved Humira presentations, including: 40mg prefilled pen, 40mg prefilled syringe, 20mg prefilled syringe, 10mg prefilled syringe, and 40mg single-use glass vial. Currently, users are instructed that Humira must be refrigerated at 36°F to 46°F (2°C to 8°C). The proposed label change will allow storage of Humira up to 77°F (25°C) for a single instance of up to 14 days. Humira will have to be discarded if it is not used within the 14-day period.

The Applicant notes that the potential benefit of limited room temperature storage is one of convenience, affording patients improved flexibility in special situations, such as when

traveling or otherwise absent from home, where refrigeration is either not practical or possible.

4. CMC/Device

The Center for Device and Radiological Health (CDRH) reviewed functional tests performed on the prefilled syringe (PFS) and prefilled pen. For the pre-filled syringe, the Applicant submitted a description of a real time post-shelf life study. This test exposed the prefilled syringe to 24 months of 2-8°C for up to 4 weeks and at nominal 30°C for up to 2 weeks. The testing then challenged the PFS to two device functional tests, including container closure and force measurement. These endpoints complied with accepted PFS performance criteria for each storage condition. For the prefilled pen, the Applicant submitted an evaluation of the autoinjector device constituent part performance after aging in separate conditions (one group aged for 2-3 weeks at 25°C and another group aged for 2-3 weeks at 2-8°C). The pre-filled pens were then subjected to basic performance tests, all of which passed, with the exception of one slightly out of specification device at the 25°C, which had a force-to-fire specification 2N greater than specification. This device was considered to be an outlier with a non-significant out-of-specification deviation.

The reviewer noted that the testing appeared to have been performed on newly manufactured devices and suggested that the Applicant should provide evidence that existing aging data accounts for the time the injector may now spend at 25°C. Specifically, CDRH recommended the Applicant provide data to support that the pre-filled pen will meet the essential performance requirements at or beyond worst case storage conditions (2-8°C and 25°C). This issue was discussed between CDRH, OBP, and DPARP. Given that the current supplement proposes a limited (14 day) room temperature storage option, which is only to be used in certain and infrequent situations, it was felt that worst case storage data for the prefilled pen were not needed to support this supplement. Further, it was noted that the devices would still be refrigerated during most of the shelf life. Thus, the Applicant was not asked to provide data regarding worst case aging. CDRH also requested that the review division assure that the PFS in the pen be evaluated for container closure integrity. [REDACTED] (b) (4) [REDACTED] and OBP did not have any concerns with container closure integrity in the context of the current supplement. Lastly, CDRH noted that uptake and injection forces the drug is subjected to during preparation and delivery may contribute to break-down of the drug substance. OBP did not have any concerns related to the drug substance in the context of the current supplement.

The Office of Biological Products (OBP) reviewed the stability data to support the proposed room temperature storage option. Stability data were provided to support all impacted presentations of Humira, including the 20 mg and 40 mg prefilled syringes, 40 mg autoinjector, and 40 mg institutional vial, for the proposed limited room temperature storage condition of $\leq 77^{\circ}\text{F}$ (25°C) for a single period of 14 days. Risks of excursions beyond the 77°F (25°C) room temperature condition were also assessed and discussed. The Applicant noted that the limited room temperature storage allowance is supported by

a combination of tightened release specifications, an analysis of historical drug product stability data against those tightened specifications, and an assessment of risk of excursions to the labeled 77°F (25°C) room temperature condition. OBP requested additional information related excursions that may exceed these temperature criteria. Specifically, OBP requested data demonstrating stability for 14 days at 40°C, including after 24 month storage at 5°C. The Applicant was also asked to provide the R² values for the linear regressions performed on the 5°C and 25°C data for the sum of (b) (4) (b) (4) regions. Lastly, the Applicant was asked to provide detailed information on the risk assessment that includes the assessment of the consequences of the changes to product quality attributes that are observed. The Applicant responded and these responses were felt to address all of the concerns. All the submitted data were felt to be reasonable to support a limited room temperature storage option.

5. Labeling

The Applicant submitted revised labeling, including changes made to the prescribing information, Medication Guide, pen instructions for use, and prefilled syringe instructions for use. See Appendix 1 for the Applicant's initially proposed labeling changes and Appendix 2 for the agreed upon labeling. In addition, statements regarding unrefrigerated expiration of Humira are included on the dose tray print mats, which the Applicant notes was recommended by the Agency on May 16, 2012. The revised labeling was reviewed by DMEPA, OBP, and the Patient Labeling Team.

In DMEPA's review, it was noted that in the previous submission, the Applicant submitted a label comprehension study that tested if the proposed storage option language could be understood in a "real-life" scenario. This study was reviewed in OSE Review #2012-190 dated April 11, 2012. While deficiencies were noted in this study, additional data were not requested. Specifically, at the end-of-review meeting, the Applicant was informed that human factors and labeling comprehension data were not needed to support the proposed limited room temperature storage option. Rather, support for the supplement should be provided from stability data.

DMEPA performed a risk assessment of the proposed labeling to identify deficiencies that might lead to medication errors. DMEPA found the addition of the proposed limited room temperature storage option acceptable for the proposed labeling (Full Prescribing Information, Medication Guide, and Instructions for Use). However, the Applicant was asked to add a space on the print mat labeling to document the data of initial removal from the refrigerator. Documentation of the date of removal is important because Humira has to be discarded within 14 days. In addition, the institutional vial label and carton labeling for all presentations was not submitted for Agency review. The Applicant made the requested change and incorporated changes to all presentations.

The Applicant was asked to add information to the prescribing information and instructions for use noting that Humira should not be exposed to extreme temperatures. In addition, the Applicant was asked to provide data that Humira could be taken in and out of the refrigerator, as noted in the proposed labeling. These data were provided and felt to be reasonable by OBP.

The Applicant also proposes that language be added to the prescribing information and patient package insert allowing warming of the Humira drug product prior to injection. To support this change, the Applicant submitted data regarding the time required for Humira to reach room temperature from storage temperature (2 to 8°C) in the various packaging presentations (2.3.P.2). The warm-up times to achieve 20°C were 6-8 minutes for PFS, 9-15 minutes for autoinjector, and 10-13 minutes for vial. The Applicant notes that these data support labeling instructions to allow Humira presentations to warm-up for 15-30 minutes prior to use. The Applicant also proposed labeling changes to note that (b) (4), but did not provide specific clinical data related to this.

Reviewer's comments: While the Applicant has provided data regarding the time required to warm Humira, the Applicant has not provided data support the conclusion that (b) (4)

Thus, the labeling text will be modified to indicate that warming can be performed if it is more comfortable for the patient, rather than (b) (4)

Additional modifications were recommended by the Patient Labeling change to improve the clarity of the labeling and for consistency with current labeling practice. These modifications were incorporated by the Applicant. See Appendix 2 for the final agreed upon labeling.

6. Summary of Changes and Recommendations

This review evaluates proposed modifications made by the Applicant to change the Humira storage instructions to allow for a limited room temperature storage option for the Humira prefilled syringes, Humira pen (autoinjector), and Humira institutional vial presentations. Specifically, the proposed label change will allow storage of Humira up to 77°F (25°C) for a single instance of up to 14 days. The changes would apply to all five of the currently approved Humira presentations (10mg prefilled syringe, 20mg prefilled syringe, 40mg prefilled syringe, 40mg pen, and 40mg institutional vial). According to the Applicant, the patient benefit of a limited room temperature storage option is one of convenience, affording patients improved flexibility in special situations, such as when traveling or otherwise absent from home, where refrigeration is either not practical or possible.

The Applicant submitted revised labeling, including changes made to the prescribing information, Medication Guide, Pen instructions for use, and prefilled syringe instructions for use.

The primary data to support this supplement comes from stability data with associated updated labeling. These data and labeling changes were felt to be reasonable by all reviewing disciplines. Thus, our recommendation is approval of this supplement.

6.1 Recommended Regulatory Action

The recommended regulatory action is approval of this supplement.

Appendix 1: Highlights of proposed labeling revisions:

PI

2.7 General Considerations for Administration



16 HOW SUPPLIED/STORAGE AND HANDLING

Storage and Stability



PPI

How should I store HUMIRA?



(b) (4)

(b) (4)

(b) (4)

Appendix 2: Final labeling

81 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/

JANET W MAYNARD
12/23/2014

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
BLA 125057/S-280

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 16, 2012, 2012
To: File for STN: 125057/280
Labeling: Kimberly Rains
RPM: Andrew Shiber
From: Jun Park, Ph.D., Product Reviewer, DMA/OBP/CDER, HFD-123
Through: Ruth Cordoba-Rodriguez, Ph.D., Team Leader, DMA/OBP/CDER
Patrick Swann, Ph.D., Division Deputy Director, DMA/OBP/CDER
Applicant: Abbott Laboratories
Product: Humira[®] (adalimumab)
Supplement Receipt Date: October 29, 2010
Filing Action Date: December 29, 2011 **Status:** Complete Response
Action Due Date: April 27, 2012

SUMMARY: This PAS is to obtain approval for

- 1) **Implementation of new Cation Exchange HPLC (CEX-HPLC) release specifications for Adalimumab drug substance (DS) and for Adalimumab Single Dose Syringe, 40 mg/0.8 mL and 20 mg/0.4 mL drug products (DP)**
- 2) **Label change to allow storage of Humira[®] (adalimumab) up to 25°C (77°F) for a single period of up to 14 days.**

RECOMMENDATION

We have completed the review of this supplement and have determined that

- 1) Proposed CEX-HPLC release specifications for adalimumab DS and DP are acceptable.
- 2) The proposed label change to allow storage of Humira[®] (adalimumab) up to 25°C (77°F) for a single period of up to 14 days is not acceptable from the product quality perspective.

Therefore, we cannot approve this supplement in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

- 1) Storage of biologic products under controlled room temperature conditions is unusual and there is great concern over the ability of patients to consistently maintain the product within the validated storage temperature (≤ 25 °C). Provide all available information with regard to how controlled room temperature will be maintained and monitored by the patient. Include information/data which adequately support that control over the controlled room temperature by the patient is sufficient to assure product will be stored within its validated storage temperature.
- 2) Please provide a risk assessment for temperature excursions beyond controlled room temperature while drug product is under patient control.

Conclusions:

- I. Recommendation: **Complete Response**
- II. Sections Deferred to other reviewers: None
- III. Post-marketing commitments: None
- IV. Future Inspection Items: None

cc:

Park/Cordoba-Rodriguez
BMAB reviewer: Bo Chi
OBP Drive:
DMA Drive
DMA Paper Files

HFD-123
HFD-328
via M. Welschenbach
BLA (STN: 125057/280)
BLA (STN: 125057/280)

REVIEW:

1. Implementation of New CEX-HPLC Release Specifications for DS and DP

a. DS Release Specifications

A summary of the proposed updated CEX-HPLC specifications and the originally-approved specifications are provided in Table 1.

Table 1. Drug Substance Specifications for Cation Exchange HPLC

(b) (4)



Drug substance release results for (b) (4) CEX-HPLC from the (b) (4) manufacturing processes are presented in Tables 2-5 reported as the average (b) (4) standard deviation and range.

Table 2. Summary of Release Testing Results for (b) (4) by Cation Exchange Chromatography

(b) (4)



Table 3. Summary of Release Testing Results for (b) (4) by Cation Exchange Chromatography

(b) (4)



Table 4. Summary of Release Testing Results for (b) (4) by Cation Exchange Chromatography

(b) (4)

Table 5. Summary of Release Testing Results for (b) (4) by Cation Exchange Chromatography

(b) (4)

Reviewer's Assessment: Abbott also has submitted the CEX-HPLC testing results for all 296 batches manufactured by the (b) (4) manufacturing processes in the PAS submission and found that the testing results analyzed met the updated release specification limits.

These are acceptable.

b. DP Release Specifications

A summary of the proposed updated CEX-HPLC specifications and the originally-approved specifications are provided in below Table 1.

Table 1. Originally Approved and Updated Bulk Pre-filled Syringe Drug Product Specifications for Cation Exchange HPLC¹

(b) (4)

A summary of testing results for the CEX-HPLC data for the release of (b) (4) of bulk pre-filled syringe adalimumab drug product is listed in Table 2. These (b) (4) adalimumab pre-filled syringe (PFS) batches were manufactured at the (b) (4)

(b) (4) between November 2002 and May 2011, including (b) (4) manufactured at the Abbott Biotechnology, Limited small volume parenteral (ABL SVP) facility in Barceloneta, Puerto Rico, between October 2010 and May 2011. The values of average (b) (4) standard deviation as well as the observed range for each parameter are reported.

Table 2. Results of the Adalimumab Drug Product Historical Batch Analysis for CEX-HPLC

(b) (4)

Reviewer's Assessment: Although Abbott didn't submit the CEX-HPLC testing results for all (b) (4) adalimumab DP PFS batches in the PAS submission, they stated that these DP testing results analyzed met the updated release specification limits.

These are acceptable.

TL comment: It is noted that the original release specification for drug product testing by CEX-HPLC had (b) (4). The proposed specification includes limits for (b) (4) of the CEX chromatogram. The proposed specification then provides a higher level of control over charge variants. I agree with the reviewer's assessment.

2. Label Change to Allow Storage of Humira® (Adalimumab) Up To 25°C (77°F) for A Single Period of Up To 14 Days.

In this PAS submission, Abbott has proposed a label change to allow storage of Humira® (adalimumab) up to 25°C (77°F) (room temperature) for a single period of up to 14 days, in addition to the approved 24 months shelf life at 5°C.

To provide justification for the for short-term room temperature storage allowance, Abbott has used

- Historical stability data for adalimumab stored at the accelerated storage condition of 25°C
- Data from a real time post-shelf life stability study that has been conducted with four batches of adalimumab 50 mg/mL PFS product. These product batches, which were previously stored at 5°C until the end of the approved 24 months shelf life, were transferred to 25°C storage for up to 28 days and 30°C storage for up to 14 days.

a. **Historical Stability Data for adalimumab stored at the accelerated storage condition of 25°C**

CEX-HPLC is the most sensitive method to monitor chemical stability of the adalimumab drug product. A typical chromatogram of CEX-HPLC is shown in Figure 1, illustrating the low amount of (b) (4) formed at 5°C storage compared to that formed at accelerated and stressed storage conditions (25°C and 40°C, respectively). Corresponding data for the primary PFS stability batch 180100AL is presented in Table 2. Significant changes of drug product were seen at 40°C after 3 months storage: whereas adalimumab drug product is at the edge of shelf life specifications after 3 months storage at 25°C. The (b) (4) formed under stressed conditions were demonstrated to be adalimumab and **to retain their TNF binding characteristics.**

Figure 1. Typical CEX-HPLC chromatograms of Adalimumab drug product (pre-filled syringe) stored for 3 months at 5, 25 and 40°C



Table 2. Sum of (b) (4) (area %) determined by CEX- HPLC after storage of primary stability batch 180100AL for 3 months at 5, 25 or 40°C

| Parameters | +5°C | +25°C | +40°C |
|------------|---------|---------|---------|
| (b) (4) | (b) (4) | (b) (4) | (b) (4) |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

Size Exclusion HPLC (SE-HPLC) is used to monitor change of the adalimumab drug product in forms of aggregates and fragments as shown in Figure 2. Obvious changes of drug product are seen at 40°C after 3 months storage with increases in both aggregations and fragments. **The 25°C samples after 3 months of storage show tendency to increase in aggregates and slight change in fragments (Figure 2), but still meet the stability specifications.**

Figure 2. Typical SE-HPLC chromatogram of adalimumab drug product stored for 3 months at 5, 25 and 40°C



Reviewer's Assessment: Abbott has showed that the CEX-HPLC is the most sensitive stability indicating method to monitor change of the adalimumab drug product stored at 25°C. Abbott further conducted statistical analysis for the CEX-HPLC stability stored at the accelerated condition (25°C).

For the decrease of adalimumab (b) (4) as well as the increase of the adalimumab (b) (4), statistical analysis was performed using the pooled data from the historical bulk PFS batches listed in Table 1 in the submission. Figures 5 and 6 show the statistical analysis results.



The result of these analysis support a shelf life of 1.75 months for an adalimumab batch that is stored at 25°C, since the 95% lower confidence interval for the linear regression line of these pooled data intersects the shelf life specification of $\geq 75\%$ for the (b) (4) and the shelf life specification of $\leq 16\%$ for the (b) (4) at the 1.75 month interval.

In addition, regression analyses were also performed on the normalized (b) (4), (b) (4) and (b) (4) data. The results indicated an adalimumab product stability of 3.0 months, 3.3 months and 4.8 months at 25°C. These results indicated that the (b) (4) and the (b) (4) are also the major limiting factors on product stability at 25°C.

A comprehensive assessment of all the stability data, in particular the 3 month time points from 25°C storage, and 36 month data from 5°C storage was performed and the results are summarized in Table 5.

Table 5. Assessment of Other Stability Testing Parameters

| Test Parameters | 5°C/36 months (n=63) | 25°C/ 3 months (n=71) |
|-----------------------------|---|---|
| Clarity | Pass* | Pass |
| Color | Pass | Pass |
| pH | Pass | Pass |
| Protein Content | Pass | Pass |
| Visible Particles | Pass | One batch failed visual score criteria ^b |
| Subvisible particles | Pass | Pass |
| In Vitro TNF Neutralization | Pass | Pass |
| Microbiological Quality | Pass | NA |
| Container Integrity | Pass | NA |
| Force Measurements | One batch failed individual force criteria ^a | Pass |
| CEX-HPLC | Pass | As expected, some results failed criteria |
| SE-HPLC | Pass | Pass |

* Pass = pass the corresponding 24 months shelf life criteria for the adalimumab.

^aBatch 070339A has an individual force value of (b) (4) of the 5°C 36 months sample. (Shelf life specification = (b) (4))

^bBatch 211389A showed a visual score of (b) (4) of the 25°C 3 months sample. (Shelf life specification = (b) (4))

Reviewer's Assessment: I believe that Abbott's statistical analysis of historical stability data for adalimumab stored at 25°C was well conducted to demonstrate that the adalimumab DP in PFS format is stable up to 1.75 month at the accelerated condition of 25°C. Abbott also showed that all the stability data conducted so far, in particular the 3 month time points from 25°C storage met the shelf life stability specifications, except stability data for the CEX-HPLC.

Abbott has used the historical stability data to demonstrate that adalimumab DP in PFS is stable up to 1.75 months at 25°C.

b. A Real Time Post-Shelf Life Stability Study

A real time post-shelf life stability study has been conducted with **four batches** of adalimumab 50 mg/mL PFS product. **These product batches, previously stored at 5°C until the end of the approved 24 months shelf life**, were transferred to 25°C storage for up to 28 days and 30°C storage for up to 14 days.

Table 6 shows storage conditions, sampling time intervals and test methods used at each time point.

Table 6. Stability Study Matrix

| Test | T0 | 25 °C | | | | 30 °C | |
|-----------------------------|----|-------|-----|-----|-----|-------|-----|
| | | 7d | 14d | 21d | 28d | 7d | 14d |
| Clarity | X | - | X | - | X | - | X |
| Color | X | - | X | - | X | - | X |
| pH | X | - | X | - | X | - | X |
| Protein Content | X | - | X | - | X | - | X |
| CEX-HPLC | X | X | X | X | X | X | X |
| SE-HPLC | X | X | X | X | X | X | X |
| TNF Neutralization | X | X | X | X | X | X | X |
| Force Measurement | X | - | X | - | X | - | X |
| Visible Particulate | X | - | X | - | X | - | X |
| Sub-visible Particulate | X | - | X | - | X | - | X |
| Container Closure Integrity | - | - | X | - | X | - | X |

X: testing scheduled/performed

- :no testing planned/performed

The results of this real time stability study for the 4 batches are summarized in the Appendix IV of the submission (not shown here). Batch 80401XH testing results are listed below as an example.

Results recording batch: 80401XH

| Test | Specification | 25°C/ 60RH | | | | 30°C/ 65RH | |
|------|---------------|------------|----|-----|-----|------------|----|
| | | t0 | 7d | 14d | 21d | 28d | 7d |

Appearance and description

| | |
|----------------------------|---------|
| Description | (b) (4) |
| Clarity | |
| Color | |
| Quantity | |
| Protein content (UV 280nm) | |

Potency

In vitro TNF neutralization (cytotoxicity test)

| | |
|---------|---------|
| (b) (4) | (b) (4) |
| (b) (4) | |

Purity

Cation exchange- HPLC (CEX-HPLC)

| | |
|---------|---------|
| (b) (4) | (b) (4) |
|---------|---------|

Pharmaceutical tests

| | |
|--|---------|
| Particulate matter (visible particles) | (b) (4) |
|--|---------|

Particulate matter (sub visible particles)

| | |
|---------|---------|
| (b) (4) | (b) (4) |
|---------|---------|

General tests

| | | | | | | | | |
|----|---------|-----|---------|-----|---------|-----|---------|-----|
| pH | (b) (4) | 5.2 |
|----|---------|-----|---------|-----|---------|-----|---------|-----|

All results for both temperature conditions and for all time points for all the 4 batches passed the shelf life specifications. Clarity, color, pH, protein content, TNF neutralization, force for the PFS, visible and sub-visible particle results barely showed a stability trend. SE-HPLC monomer showed a minimal change within (b) (4)

CEX-HPLC showed comparable degradation trends and rates for (b) (4) when compared to the corresponding data from historical stability batches as demonstrated in Figure 7 through 10.

Figure 7. CEX-HPLC (b) (4) Normalized stability results for storage at 25°C (real time and historical data combined)



Figure 8. CEX-HPLC (b) (4) Normalized stability results for storage at 25°C (real time and historical data combined)



Figure 9. CEX-HPLC (b) (4) Normalized stability results for storage at 25°C (real time and historical data combined)



Figure 10. CEX-HPLC Peak between (b) (4) Normalized stability results for storage at 25°C (real time and historical data combined)



This real time stability study demonstrated that degradation measured by CEX-HPLC at 25°C for adalimumab is comparable to the historical degradation shown for material stored at similar conditions (after storage for at least 24 months at 2-8°C). Study results further confirmed the estimated allowable (b) (4) room temperature

Reviewer's Assessment: I found that Abbott's statistical analysis of historical stability data for adalimumab stored at 25°C as well as data from the real time stability study using 4 batches of adalimumab DP batches have demonstrated that the adalimumab 50 mg/mL prefilled syringe drug product is stable up to 14 days up to 25°C before product administration.

These are acceptable from CMC perspective.

Draft Label for Humira Proposed in the Supplement:**Storage and Stability**

(b) (4)

Reviewer's Comment: The following comment will be addressed in the second review cycle for this supplement:

(b) (4)

TL comment: *Abbott states in their stability summary conclusions that the combined data presented for the long-term storage (5 °C) condition, and the real time post-shelf life stability study, in addition to the tighter CEX-HPLC specifications justify a short-term, optional room temperature (≤ 25 °C) storage of the product for up to (b) (4) before the product is administered by the end user. Abbott then calculates that an optional storage of product at room temperature (≤ 25 °C) for 14 days could be allowed to the patient/end user including the following additional allowances:* (b) (4)

The issue with Abbott's proposal related to the optional temperature storage was discussed during Divisional meeting and it was recommended that Abbott should provide better assurances that the end user will comply and understand the label instructions. It is unclear how the end user will make sure that the optional storage will be kept within the recommended temperature limit. A complete response is recommended for this supplement (see recommendations above).

In addition, any significant labeling changes will need to be cleared by the impacted CDER clinical division.

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/s/

JUN T PARK
04/20/2012

RUTH V CORDOBA RODRIGUE
04/20/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
BLA 125057/S-280

MICROBIOLOGY REVIEW(S)



Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 3/8/2012
To: Administrative File, STN 125057/280
From: Bo Chi, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB
Endorsement: Patricia Hughes, Ph.D., Team leader, CDER/OC/OMPQ/DGMPA/BMAB
Subject: Review (PAS): For the modification of storage instructions to allow limited storage of the Humira pre-filled syringe and Humira pen presentations at room temperature, plus a label change to allow storage of Humira up to 25°C for single period of up to 14 days can be supported.
Applicant: Abbott Laboratories
US License: 0043
Facility: Abbott Biotechnology Ltd.
Barceloneta, Puerto Rico 00617
FEI: 3004620772
Abbott GmbH & Co. KG
Ludwigshafen, Germany 67061
FEI: 3002807401
Product: Humira® (adalimumab)
Indication: Treatment of rheumatoid arthritis, JIA, Psoriatic arthritis, Ankylosing Spondylitis, Crohn's Disease, and Plaque Psoriasis
Dosage form: 40 mg/0.8 mL, 20 mg/0.4 mL, subcutaneous injection
PDUFA date: April 29, 2012

Recommendation: This submission is recommended for approval from a CMC sterility assurance and microbiology product quality perspective.

Review Summary

Abbott Laboratories has submitted this PAS "for the modification of storage instructions to allow limited storage of the Humira pre-filled syringe and Humira pen presentations at room temperature, plus a label change to allow storage of Humira up to 25°C for single period of up to 14 days." The limited room temperature storage option intends to provide flexibility to patients during traveling or other situations when a refrigerator is not available.

Review

A real time post-shelf life stability study using four humira 50 mg/mL pre-filled syringe (PFS) lots was conducted to support the short-term room temperature storage. The PFS lots were

stored at 5°C until the end of the approved 24 months shelf life and were then transferred to 25°C for up to 28 days and 30°C for up to 14 days. An approved dye ingress test was used in the real time post-shelf life stability study to demonstrate that the integrity of the PFS is not affected by the short-term room temperature storage. The dye ingress test was conducted on day 14 and day 28 for PFS stored at 25°C and on day 14 for PFS stored at 30°C. Report D 018904 E01 showed that all the dye ingress test results met the acceptance criteria for all the lots included in the study.

The submission proposed the following storage period at room temperature:

Table 7. Recommendations for storage of adalimumab 50 mg/mL pre-filled syringe drug product at room temperature ($\leq 25^{\circ}\text{C}$) during manufacturing and distribution and before administration by the end user

| Type of Allowance | Room Temperature ($\leq 25^{\circ}\text{C}$) Storage/Exposure Period |
|--|--|
| (b) (4) | |
| Optional storage of packaged PFS or pen drug product by the end user | Not to exceed 14 days prior to administration |

Reviewer comment: The proposed storage time at room temperature does not affect the integrity of the PFS and therefore, there is no impact on the sterility of the drug product. Information and data not related to sterility assurance of the product should be reviewed by the DMA reviewer.

Satisfactory

Environmental Assessment:

The supplement did not involve the introduction of a new unlicensed molecular entity or an increase in the production of the previously licensed drug substances; therefore, Environmental Assessment information is not required.

cGMP Status:

PAS, STN125057/280, Abbott Laboratories, Humira

Abbott Biotechnology Ltd., Barceloneta, Puerto Rico 00617
FEI: 3004620772

Inspected by SJN-DO March 18-29, 2011 and classified VAI. This was a routine GMP surveillance inspection. The CBI and TRP profiles are currently acceptable.

Abbott GmbH & Co. KG, Ludwigshafen, Germany 67061
FEI: 3002807401

Inspected by IOG December 11-17, 2009 and classified VAI. The was a PAI and GMP inspection. The CTL profile was updated and is acceptable.

Conclusion

- I. The supplement is recommended for approval from a CMC sterility assurance and microbiology product quality perspective.
 - II. The label changes and data and information not related to sterility assurance should be reviewed by DMA reviewers.
 - III. No inspectional follow up items were identified.
- Cc: WO 51, Chi
WO 51, Hughes
HFD-123, Shiber

Archived File: S:\archive\BLAs\125057\125057.280.rev.mem.PAS.3.8.2012

From: [Pohlhaus, Timothy](#)
To: [Chi, Bo](#);
cc: [Pohlhaus, Timothy](#); [CDER-TB-EER](#);
Subject: Final TB-EER response - Abbott PAS STN125057/280
Date: Thursday, March 08, 2012 3:47:47 PM

The Division of Good Manufacturing Practice Assessment has completed its review and evaluation of the TB-EER for STN 125057/280. Please see below for individual site compliance statuses. There are no pending or ongoing compliance actions that prevent approval of this supplement.

Timothy J. Pohlhaus, Ph.D.

Interdisciplinary Scientist, Chemist
Food and Drug Administration
CDER/OC/OMPQ
10903 New Hampshire Avenue
Building 51, Room 1333
Silver Spring, MD 20993
Phone - (301) 796-5224

From: Chi, Bo
Sent: Tuesday, March 06, 2012 2:49 PM
To: CDER-TB-EER
Subject: Final TB-EER for Abbott's PAS STN125057/280

Hi,
Please provide a TB-EER for Abbott's PAS STN125057/280 for the facilities listed below: For the modification of storage instructions to allow limited storage of the Humira pre-filled syringe and Humira pen presentations at room temperature, plus a label change to allow storage of Humira up to 25°C for single period of up to 14 days can be supported. The PDUFA date is 4/29/2012.

The stability tests are conducted in these facilities:
Abbott Biotechnology Ltd.
Road No. 2, Km. 59.2
Barceloneta,
Puerto Rico 00617

FEI: 3004620772

Inspected by SJN-DO March 18-29, 2011 and classified VAI. This was a routine GMP surveillance inspection. The CBI and TRP profiles are currently acceptable.

Abbott GmbH & Co. KG
Knollstrasse
Ludwigshafen,
Germany 67061
FEI: 3002807401

(b) (4)

Inspected by IOG December 11-17, 2009 and classified VAI. The was a PAI and GMP inspection. The CTL profile was updated and is acceptable.

Thanks,
Bo

Thanks

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/s/

BO CHI
03/12/2012

PATRICIA F HUGHES TROOST
03/13/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
BLA 125057/S-280

OTHER REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: December 22, 2014

To: Badrul Chowdhury, M.D., Ph.D.
Director
**Division of Pulmonary, Allergy and Rheumatology
Products (DPARP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Robin Duer, MBA, BSN, RN
Acting Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Aman Sarai, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Focused Review of Patient Labeling: Medication Guide
(MG) and Instructions for Use (IFUs)

Drug Name (established name): HUMIRA (adalimumab)

Dosage Form and Route: Injection, for subcutaneous use

Application Type/Number: BLA 125057

Supplement Number: 280

Applicant: AbbVie Inc.

1 INTRODUCTION

On December 29, 2011 AbbVie, Inc. submitted for the Agency's review a supplemental BLA (S-280) for HUMIRA (adalimumab) providing modifications for the approved storage instructions. The Agency issued a Complete Response for S-280 on April 27, 2012. Abbvie Inc. requested an extension of this application until July 27, 2014.

On June 26, 2014, AbbVie, Inc. submitted a Complete Response for S-280. This submission includes a change to the HUMIRA (adalimumab) storage instructions to allow a limited room temperature storage option.

HUMIRA (adalimumab) was originally approved on December 31, 2002 and is indicated for:

- 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 2 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.
- Adult 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.
- Pediatric Crohn's Disease: Reducing signs and symptoms and inducing and maintaining clinical remission in patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate.
- 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 systemic therapies are medically less appropriate.

This focused review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Division of Pulmonary, Allergy and Rheumatology Products (DARP) on August 18, 2014 for DMPP to provide a focused review of the Applicant's proposed Medication Guide (MG) and

Instructions for Use (IFUs) for HUMIRA (adalimumab), injection for subcutaneous use.

2 MATERIAL REVIEWED

- Draft HUMIRA (adalimumab) MG and IFUs received on June 26, 2014, revised by the Review Division throughout the review cycle and received by DMPP on December 18, 2014.
- Draft HUMIRA (adalimumab) Prescribing Information (PI) received on June 26, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on December 18, 2014

3 REVIEW METHODS

In our focused review of the MG and IFUs we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFUs are consistent with the Prescribing Information (PI)
- added DMPP comments and revisions within the MG and IFU text (highlighted in yellow) as requested by DPARP since the comments review tool was disabled

4 CONCLUSIONS

The MG and IFUs are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our focused review of the MG and IFUs is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFUs.

Please let us know if you have any questions.

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/s/

ROBIN E DUER
12/22/2014

LASHAWN M GRIFFITHS
12/22/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

MEMORANDUM



Food and Drug Administration
Center for Devices and Radiological Health

Date: October 21, 2014

From: Ryan McGowan, Biomedical Engineer
CDRH/ODE/DAGRID/GHDB

To: Sadaf Nabavian, Pharm.D.
CDR, U.S Public Health Service
Senior Regulatory Project Manager
FDA/CDERII/OND/DPARP
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: CDER BLA 125057-S280; CDRH ICC1400542

I. Purpose

To provide CDER/DPARP with a memorandum which documents review of device constituent part attributes of BLA 125057-S280 content related to changes in combination storage practice.

II. Proposed Drug Indications

This submission is not associated with a change in indications. The sponsor is seeking to continue marketing each of the approved indications for Humira.

III. Review Documents

Electronic Review Document for BLA 125057-S280 (sequence 0304)

IV. Background and Purpose of Submission

The purpose of this supplement is to request approval for a change to the Humira storage instructions to allow a room temperature storage option for the Humira prefilled syringes, Humira Pen, and Humira vial presentations. The proposed label change, if approved in its proposed form, will allow storage of Humira up to 77°F (25°C) for a single instance of up to 14 days.

According to the sponsor, the patient benefit of a limited room temperature storage option is one of convenience, affording patients improved flexibility in special situations, such as when traveling or otherwise absent from home, where refrigeration is either not practical or possible.

In December 2011, the sponsor submitted a request for the identical change in storage instructions (sBLA 125057/280 (eCTD sequence 0111) dated 29 December 2011). In response the Agency provided a “complete response” along with several deficiencies related to stability information and labeling information. According to the sponsor, they have held interim meetings with the Agency to reach agreement

on the content of the combination product label and the necessary stability testing required achieving the storage claim (End of Review (Type C) Meeting request (eCTD sequence 0237) on 18 September 2013 and Meeting Information Package (eCTD sequence 0257) accompanying the Type C meeting request.

V. Review of Prior BLA Submissions and Meetings

The consultant examined the electronic document record for the original BLA supplement and meeting minutes related to the stability testing cited by the sponsor. Based on review of sBLA 125057/280 (eCTD sequence 0111), End of Review (Type C) Meeting request (eCTD sequence 0237), and Meeting Information Package (eCTD sequence 0257), it does not appear that any examination or questions related to device information for the combination product has been examined.

VI. Review of Device Stability Information

Reviewer Note: This review is intended to cover potential effects on the device constituent parts (prefilled syringe and auto-injector) which may be derived from the change in storage conditions requested. This review will not cover any elements of drug stability within any presentation, microbial ingress protection, and will also not cover any functionality of the container closure vial presentation.

The Sponsor wishes to alter the current combination product storage information. Previously, users were instructed that HUMIRA must be refrigerated at 36°F to 46°F (2°C to 8°C). The sponsor now wishes for the product to be stored up to 77°F (25°C) for a single instance of up to 14 days. This affects presentations available in vial, prefilled syringe, and vial.

Pre-filled Syringe (PFS) Stability

Submission section 3.2.P.8.1 contains a description of a real time post-shelf life study on the pre-filled syringe presentation. This test, conducted under protocol (b) (4), exposed the PFS to 24 months of 2-8°C then stored the PFS 25°C for up to 4 weeks (28 days) and at nominal 30°C for up to 2 weeks (14 days). This testing then challenged the PFS to two device functional tests, including container closure and force measurement. These endpoints complied with accepted PFS performance criteria for each storage condition.

One test, intended to validate the CEX-HPLC method, showed that 5°C /36 months aged samples deviated from allowable force measurements, providing an individual force value of (b) (4). This is considered an outlier, as this is an experience with a single PFS, not a mean batch value. Additionally, no container closure breaches were noted within the same batch, and so the primary hazard of a damaged or out of specification PFS was not realized within the batch.

Pre-filled Pen (PFP) Stability

Submission section 2.3.P.8 contains an evaluation of auto-injector device constituent part performance after aging in separate conditions (one group aged for 2-3 weeks at 25°C and another group aged for 2-3 weeks at 2-8°C). The PFPs were then subjected to basic performance tests, all of which passed, with the exception of one slightly out of specification device at the 25°C which had a force-to-fire specification (b) (4) greater than specification. This device is considered to be an outlier with a non-significant out-of-specification deviation.

The subject test described appears to have been performed on newly manufactured devices. This testing does not account for pre-aging at a temperature condition of 2-8°C for 24 months. The reviewer does not

expect that exposure of the device to a temperature of 25°C for a period of 21 days during the lifetime of the injector would adversely affect the mechanics of the device. However, the firm should be asked to supply evidence that existing aging data accounts for the time the injector may now spend at 25°C.

Additionally, the sponsor does not appear to have conducted testing on the integrity of the primary closure (PFS) imbedded in the PFP. The sponsor should be requested to confirm that the (b) (4) presentation and that the assembly process is not believed to impact the contain closure.

Drug Product Assessment After In-use Testing

The submission does not appear to contain detailed protocol documents, and so the reviewer is not aware if the drug samples used for assessment of drug stability to support the new storage instructions were delivered in a manner consistent with each presentation. The reviewer is concerned that the uptake and injection forces the drug is subjected to during delivery may contribute to break-down of the drug substance; this factor should be accounted for within the testing.

VII. CDRH Recommendations for DPARP

1. To support the stability of the pre-filled injector presentation, the sponsor has provided testing which appears to compare newly produced injectors aged for 2-3 weeks at two temperature conditions (2-8°C and 25°C). This testing is adequate to demonstrate that the injector is not expected to perform differently at these temperatures, however it does not assess functionality of the injector at worst case aging (23.25 months at 2-8°C and .75 months at 25°C). The firm should provide evidence that stability testing previously completed has accounted for this storage condition. CDRH recommends the following IR be issued to the sponsor:

Submission section 2.3.P.8 contains a summary of testing on the pre-filled pen combination product. This testing appears to compare newly manufactured injectors aged for 2-3 weeks at two different temperature conditions (2-8°C and 25°C). This testing is adequate to demonstrate that the injector does not perform differently at these two temperatures, however it does not assess functionality of the injector at worst case aging (23.25 months at 2-8°C and .75 months at 25°C). Provide evidence which supports that the pre-filled pen will meet essential performance requirements at or beyond this worst case storage condition.

2. The sponsor does not appear to have conducted testing on the integrity of the primary closure (PFS) imbedded in the PFP. The reviewer is also unable to locate information within the submission which confirms that the (b) (4) presentation and that the PFP assembly process is not believed to impact the PFS contain closure. The reviewer recommends that the review division assure that the PFS located within the PFP has been evaluated for container closure integrity; however CDRH defers review of this area to the review division.
3. The submission does not appear to contain detailed protocol documents, and so the reviewer is not aware if the drug samples used for assessment of drug stability to support the new storage instructions were delivered to the stability test setup in a manner consistent with clinical delivery of each presentation. The reviewer is concerned that the uptake and injection forces the drug is subjected to during preparation and delivery may contribute to break-down of the drug substance. The reviewer recommends that the review division assure that any potential effects of uptake or

injection after aging have been evaluated; however CDRH defers review of this area to the review division.

VIII. Concurrence Table

| Concurrence Party | Signature |
|-------------------|--|
| Reviewer | <p>Ryan J. Mcgowan -S</p> <p>Digitally signed by Ryan J. Mcgowan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000352462, cn=Ryan J. Mcgowan -S Date: 2014.10.22 17:13:44 -04'00'</p> |
| Team Leader | <p>Alan M. Stevens -S</p> <p>Digitally signed by Alan M. Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300189211, cn=Alan M. Stevens -S Date: 2014.10.23 09:13:18 -04'00'</p> |
| Branch | <p>Richard C. Chapman -S</p> <p>Digitally signed by Date: 2014.10.23 14:05:02 -04'00'</p> |

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/s/

SADAF NABAVIAN
10/24/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: October 10, 2014

Requesting Office or Division: Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Application Type and Number: BLA 125057 S-280

Product Name and Strength: Humira (adalimumab)
Injection
40 mg/0.8 mL prefilled pen, prefilled syringe, & vial
20 mg/0.4 mL prefilled syringe

Product Type: Combination Product (Drug + Device)

Rx or OTC: Rx

Applicant/Sponsor Name: AbbVie, Inc.

Submission Date: June 26, 2014

OSE RCM #: 2014-1713

DMEPA Primary Reviewer: Teresa McMillan, PharmD

DMEPA Team Leader: Kendra Worthy, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed labeling {Full Prescribing Information (PI), Medication Guide, and Instructions for Use (IFU)} as well as the printmat labeling for BLA 125057/S-280, Humira (adalimumab) for areas of vulnerability that could lead to medication errors.

BLA 125057/S-280 received a Complete Response on April 27, 2012. The Applicant is resubmitting BLA 125057/S-280 to obtain approval for a change to the Humira storage instructions to allow a limited room temperature storage option for the Humira prefilled syringes, pen, and institutional vial presentations. The proposed labeling change will allow storage of Humira up to 77°F (25°C) for a single instance of up to 14 days. Humira will have to be discarded if not used within the 14-day period.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed. In addition, a FDA Adverse Event Reporting System (FAERS) 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, #2010-2102 and #2009-935. In addition, no errors involving storage were identified in these reviews.

| Material Reviewed | Appendix Section (for Methods and Results) |
|---|---|
| Product Information/Prescribing Information | A |
| FDA Adverse Event Reporting System (FAERS) | B-N/A |
| Previous DMEPA Reviews | C |
| Human Factors Study | D-N/A |
| ISMP Newsletters | E-N/A |
| Other | F-N/A |
| Labels and Labeling | G |

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed labeling to identify deficiencies that may lead to medication errors. We find the addition of the proposed limited room temperature storage option acceptable for the proposed labeling {Full Prescribing Information (PI), Medication Guide, and Instructions for Use (IFU)}. However, the applicant has not provided a place on the

printmat labeling to document the date of initial removal from the refrigerator. The documentation of the date of removal is important since Humira has to be discarded within 14 days. In addition, the institutional vial label and the carton labeling for all presentations was not submitted for Agency review. We provide recommendations in Section 4.1 Recommendations to AbbVie.

We also note that in the previous submission the Applicant submitted a label comprehension study which tested if the proposed storage option language could be understood when applied in a “real-life” scenario. This study contained deficiencies which were identified in OSE Review #2012-190 dated April 11, 2012. However, due to time constraints, we did not request the applicant repeat the label comprehension study. Instead, we compared the proposed language to marketed products (i.e. insulin) with similar storage options and found that the language appears to be similar.

Also, we defer to the Division to determine if the proposed storage option is safe from a sterility assurance and product quality perspective.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed labels and labeling can be improved to increase the prominence of important information on the labels and labeling to promote the safe use of the product. We provide the following recommendations in Section 4.1.

4.1 RECOMMENDATIONS FOR ABBVIE

A. All Carton Labeling and Institutional Vial Label

1. Ensure the proposed storage option language is adequately added to all carton labeling and to the institutional vial label.

B. Institutional Vial Label, All Printmat Labeling, All Carton Labeling

1. Provide a space on the institutional vial label, printmat labeling, and all carton labeling for documentation of the date of initial removal from the refrigerator.
2. Submit labels and labeling for all presentations for Agency review once recommendation A(1) and B(1) are implemented.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Humira that AbbVie Inc. submitted on June 26, 2014.

| Table 2. Relevant Product Information for Humira (Adalimumab) | |
|--|--|
| Initial Approval Date | December 31, 2002 |
| Active Ingredient | Adalimumab |
| Indication | Treatment of Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Crohn's Disease, Ankylosing Spondylitis, Psoriatic Arthritis, Plaque Psoriasis, and Ulcerative Colitis |
| Route of Administration | Subcutaneous |
| Dosage Form | Injection |
| Strength | 20 mg/0.4 mL, 40 mg/0.8 mL |
| Dose and Frequency | 10 mg, 15 mg, 20 mg, 40 mg, 80 mg, or 160 mg every other week |
| How Supplied | Single-use Prefilled syringe, Single-use Pen, Single-use vial for institutional use only |
| Storage | Refrigerated at 2°C to 8° C (36° to 46° F) and should be protected from exposure to light. |

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:Drive on September 19, 2014 using the terms, Humira and adalimumab to identify reviews previously performed by DMEPA.

C.2 Results

Our search identified one previous review¹ and our previous recommendations were not implemented. Those relevant recommendations not implemented are provided to the Applicant in Section 4.1.

¹ McMillan T. Label and Labeling Review for Humira (adalimumab) (BLA 125057). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2012 April 11. 11 p. OSE RCM No.: 2012-490.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,² along with postmarket medication error data, we reviewed the following Humira labels and labeling submitted by AbbVie on June 26, 2014.

- Carton Printmat Labeling

² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

TERESA S MCMILLAN
10/10/2014

KENDRA C WORTHY
10/10/2014

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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

Memorandum

PROJECT MANAGER'S REVIEW

Application Number: STN 125057/280
Name of Drug: HUMIRA[®] (adalimumab)
Applicant: Abbott Laboratories
Material Reviewed: HUMIRA[®] (adalimumab) Carton and Container Labels,
Prescribing Information-Description Section
Submission Date (s): December 29, 2011

Executive Summary:

The carton, container, and the Prescribing Information for HUMIRA[®] (adalimumab) was reviewed and found to conform to the applicable regulations under 21 CFR 201 Subpart A and 21 CFR 610 –Subpart G. However, recommendations to improve readability. Please see the Conclusions section for comments.

Background:

Abbott Laboratories has submitted a supplement to HUMIRA[®] (adalimumab), BLA 125057, to modify the approved storage instructions to allow limited storage (up to 14 days) of the Humira pre-filled syringe and Humira pen presentations at room temperature.

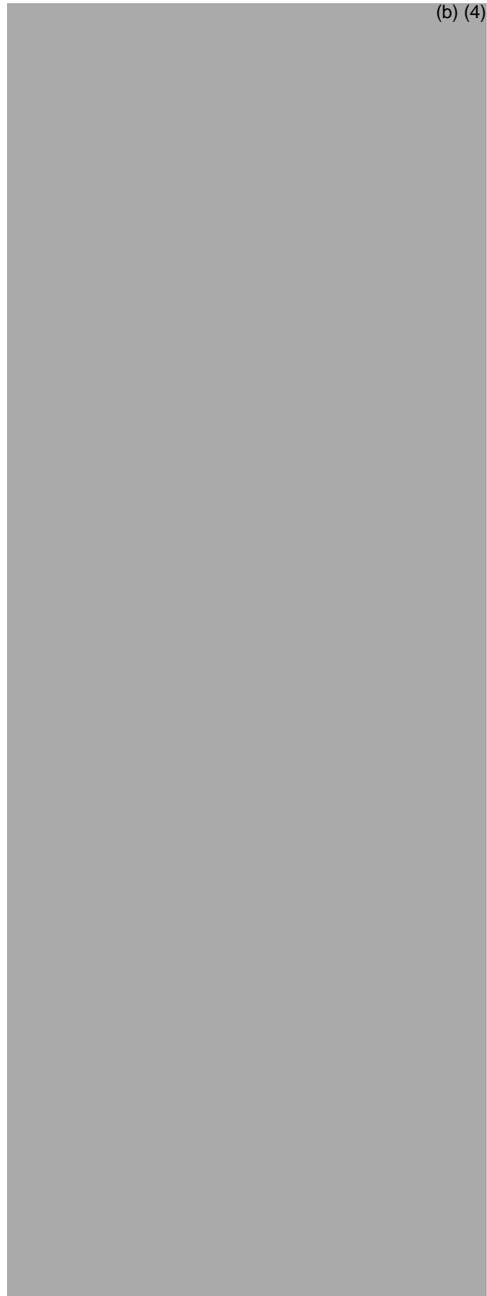
Information Reviewed:

HUMIRA[®] (adalimumab)
-Pre-filled and Pen Container labels (20 mg/0.4mL and 40 mg/0.8 mL)

REVIEW

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End of sponsor material

Conclusions:

The following recommendations for the applicant have been discussed with the Division of Medication Error Prevention and Analysis (DMEPA):

- I. Pediatric Patient formulation-Syringe (20 mg/0.4 mL)
 - a. To reduce crowding, improve legibility, and create space remove the following items from the immediate container label:

(b) (4)



* See Recommended format below

- II. Adult preparation Pen and Syringe label (40 mg/0.8 mL)
 - a. To reduce crowding, improve legibility, and create space remove the following items from the immediate container label:

(b) (4)



- See Recommended format below

- III. Carton labels
 - a. Carton labels were not submitted for review in the original submission on 12/29/2011 in sequence 0111.
- IV. Patient Package Insert
 - a. Defer to DMEPA and Patient Labeling for comment.

*Recommended format:



Kimberly Rains, Pharm.D.
Regulatory Project Manager
CDER/OPS/OBP/IOD

Comment/Concurrence:

Jun Park, Ph.D.
Product Reviewer
CDER/OPS/OBP/DMA

Patrick Swann, Ph. D.
Deputy Director
Division of Monoclonal Antibodies
CDER/OPS/OBP

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/s/

KIMBERLY M RAINS
04/23/2012

JUN T PARK
04/23/2012

PATRICK G SWANN
04/27/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

REVIEW DEFERRAL MEMORANDUM

Date: April 23, 2012

To: Steven Kozlowski, MD
Director
Office of Biotechnology Products (OBP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Melissa Hulett, MSBA, BSN, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams, MSN, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review Deferred: Medication Guide (MG)

Drug Name (established name): HUMIRA (adalimumab)

Application Type/Number: BLA 125057

Supplement Number: 280

Applicant: Abbott Laboratories

1 INTRODUCTION

On December 29, 2011 Abbott Laboratories submitted for the Agency's review a prior approval supplement for the modification of the storage instructions to allow limited storage of the Humira (adalimumab) pre-filled syringe and Humira (adalimumab) pen at room temperature and a label change to allow storage up to 25°C for a single period of up to 14 days.

Humira (adalimumab) is indicated for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's Disease, and plaque psoriasis. On February 24, 2012, the Office of Biotechnology Products (OBP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for Humira (adalimumab).

This memorandum documents the DMPP review deferral of the Applicant's proposed Medication Guide (MG) for Humira (adalimumab).

2 CONCLUSIONS

Due to outstanding biotechnology deficiencies, the Office of Biotechnology Products plans to issue a Complete Response (CR) letter regarding concern over the ability of patients to consistently maintain the product within the validated storage temperature. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

**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 Comprehension Study and Label and Labeling Review

Date: April 11, 2012

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

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

Deputy Director Kellie Taylor, PharmD
Division of Medication Error Prevention & Analysis

Drug Name(s) and Strength(s): Humira (Adalimumab)
Injection
40 mg/0.8 mL Prefilled Pen, 20 mg/0.4 mL
Prefilled Syringe, 40 mg/0.4 mL Prefilled Syringe

Application Type/Number: BLA/125057

Submission Number: 280

Applicant/sponsor: Abbott Laboratories, Inc

OSE RCM #: 2012-490

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

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1 INTRODUCTION

This review evaluates the Label Comprehension Study, the proposed blister labels, insert labeling, and the Patient Instructions for Use submitted on December 29, 2011, for Humira (Adalimumab), BLA 125057 for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND

The proposed labels and labeling are similar to the currently approved Humira Pen and Humira Pre-filled Syringe, with the addition of a new storage option to allow storage of Humira at room temperature [up to 25°C (77°F)] for a single period of up to 14 days. Once left un-refrigerated, Humira must be used within the 14 day period even if it is re-refrigerated. If Humira has not been used within the 14 day period it must be discarded.

The Label Comprehension Study assessed the adequacy of the proposed language for the new room temperature storage option. Additionally, the study evaluated if participants could take the correct action based on their understanding of the proposed language to determine the most effective, clear, and easily understood language to communicate this new storage option.

1.2 REGULATORY HISTORY

Humira was approved in December 2002 to treat rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and Crohn's disease. In 2008, two additional indications, juvenile idiopathic arthritis and plaque psoriasis, were approved.

1.3 PRODUCT INFORMATION

- Active Ingredient: Adalimumab
- Indication of Use: Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Crohn's Disease, Ankylosing Spondylitis, Psoriatic Arthritis and Plaque Psoriasis
- 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: Pre-filled syringe and Single-use Pen
- 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

DMEPA reviewed the labels, labeling and labeling comprehension study, “Humira Room Temperature Storage Language: A Report of a Formative Study for Label Language Comprehension Testing” submitted by the Applicant on December 29, 2011. DMEPA also reviewed previous label and labeling reviews (OSE Reviews #2010-1822, 2001-2102, 2009-935, for Humira to identify if any medication errors involving storage were reported.

Additionally, we evaluated the review from the Biotech Manufacturing Assessment Branch to ensure the proposed storage option was safe from a sterility assurance and product quality perspective.

2.1 LABELING COMPREHENSION STUDY

DMEPA reviewed the Label Comprehension Study, “Humira Room Temperature Storage Language: A Report of a Formative Study for Label Language Comprehension Testing” submitted by Abbott Laboratories, Inc. on December 29, 2011. When reviewing the study, we focused on identifying areas of weakness in the study design that may affect the utility of the study results. (Appendix A summarizes the Label Comprehension Study).

2.2 LABEL AND LABELING RISK ASSESSMENT

Using the principals of human factors and Failure Mode and Effects Analysis,¹ the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Blister Labels, Insert Labeling, Patient Instructions For Use submitted on December 29, 2011 (See Appendix B for blister labels, no image for insert labeling and Patient Instructions For Use)

In addition to the materials reviewed above, we evaluated similar products (i.e. other DMARD and insulin products) to ensure that the proposed language is similar to other marketed products which are typically refrigerated and may include a room temperature storage option.

3 RESULTS

The following section describes our findings of the labeling comprehension study.

3.1 LABELING COMPREHENSION STUDY

The study was conducted to assess the sufficiency of the proposed language for the new room temperature storage option (See Appendix A for the three different language Versions). Additionally, the goals of the study were to see if users understood the new room temperature storage language, to evaluate if users could correctly act based on their

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

understanding of the proposed storage option and to determine the most effective, clear, and easily understood language to state this new storage option.

Study Design

The study design involved testing two different versions of the new room temperature language in a direct comparison. One version used formal medical language and terms and the other version used “patient-friendly” language.

There were a total of 20 participants. Each participant received one of the two language versions presented on the carton labeling, blister tray label, Medication Guide, or the Patient Instructions for Use. The participants were given a closed Humira carton by the Study Moderator and were instructed to open the carton and read any of the enclosed materials in an effort to simulate “real-life” use. After reading the enclosed materials the moderator asked each participant to respond to a series of “real-life” scenarios and to answer a set of questions regarding comprehension of the instruction for use. The Data Analyst recorded participant’s behavior and verbal responses.

Participant Demographics

The participants represented a mix of ages, gender, and level of education. Additionally, participants had a diagnosis of Rheumatoid Arthritis, Crohn’s Disease, and/or Plaque Psoriasis, currently take Humira or some other Disease-modifying antirheumatic drug, currently do not take any Disease-modifying antirheumatic drug, currently self-inject, and currently do not self-inject.

Data Analysis

A performance failure was defined by three criteria if the participant chose to use Humira after it has been:

- Left out of the refrigerator for longer than 14 days
- Left out at a temperature above 77°F/25°C
- Exposed to light

The Data Analyst captured unanticipated use errors by recording any alternative answers the participants provided. Additionally, the Study Moderator asked each participant their logic in choosing a particular course of action.

Results

On Days 1 and 2 of the study, participants received one of two versions of the proposed room temperature storage language. The participants were divided into four groups (two groups of A: odd numbered participants and two groups of B: even numbered participants). Each group was assigned to either Version 1 or Version 2 of the proposed language on Days 1 and 2. However, it is unclear if all groups evaluated all versions of the proposed language because they Applicant did not distinguish between the two groups in A and B. On Day 3 of the study, the data was analyzed to identify areas of confusion and the cause of the confusion. The results showed that the participants did not find the versions vastly different from each other. Additionally, participants did not understand why the product would not require refrigeration. As a result of this

information, a third version of the proposed storage language which included a condition when Humira may require the room temperature storage option was added.

On Days 4 and 5, versions 2 and 3 of the proposed temperature storage language were tested. The participants were grouped the same as previously discussed. Additionally, it appears that the same Groups A and B that previously evaluated Version 2 on Days 1 and 2 may have evaluated Version 2 again on Days 4 and 5. The applicant concluded that after seeing version 3 of the proposed storage language, all participants understood that Humira could be left out of the refrigerator once at room temperature. Additionally, the participants understood that it must be used or discarded within 14 days. Thus, it was concluded that version 3 was demonstrated to be the most clear and comprehensible version by potential Humira users. However, one participant who read version 3 indicated that he would use Humira even if stored at room temperature for up to a month because he thinks the instructions are often overly cautious.

Additionally, we noted in the Interview Guide Version 1 and Version 2, in Question 22. “Can you tell me where you would find instructions about how to store this product?” has a note that instructs the moderator to mark the relevant sections with a sticky note to make it easy for participants to find. Also, the results for this question were not reported.

4 DISCUSSION

The following section describes the assessment of the labeling comprehension study and the associated labels and labeling.

4.1 LABEL COMPREHENSION STUDY

Our evaluation of the overall study design determined it was not adequate to conclude version 3 of the proposed language is most appropriate for users. The purpose of the study was to determine if the proposed storage language could be understood when applied in a “real-life” scenario. However, it appears participants were guided where to look for the new storage option.

The Applicant concludes that version 3 was the most clear and comprehensible. However, we are not sure how this conclusion was reached because one participant who read version 3 responded that he would use room temperature Humira for up to a month even though the labels and labeling state 14 days. Also, two other participants (unknown version used) state that they would use Humira immediately, despite being unsure about how long it was out. This shows that regardless of the language used, medication storage errors may still occur. Additionally, it appears that the same participants may have evaluated all three versions of the proposed language, which could cause the results of the study to be biased.

We realize that due to time constraints, repeating the label comprehension study may not be an option for the Applicant. Therefore, we compared the proposed language to marketed products (i.e. insulin) with similar storage options and found that the language appears to be similar. The only differences are where the information is located on the labels and labeling and the language in version 3 does not restate the “protect from light” statement. However, the location of the proposed storage language is appropriate for this product because it is presented wherever the currently approved storage requirements are

found (i.e. Blister Label, Insert Labeling, Medication Guide, Patient Instructions for Use). Thus, we find the proposed room temperature storage language appropriate except for the deficiencies noted in Section 5.1 Comments to the Applicant.

4.2 LABELS AND LABELING

The location of the proposed room temperature storage option is adequate for the labels and labeling because it is located where the currently approved storage option is. However, the proposed room temperature storage option has omitted restating the “protect from light” statement. Additionally, the Applicant has not provided a place on the blister label and the carton labeling to document the date of initial removal from the refrigerator. Thus, we find the proposed labels and labeling appropriate except for the deficiencies noted in Section 5.1 Comments to the Applicant.

5 CONCLUSIONS AND RECOMMENDATIONS

The label comprehension study and the associated labels and labeling contain deficiencies. Due to time constraints, we are not requiring the Applicant to repeat the label comprehension study; however we provide comments in Section 5.1 for implementation prior to approval of this supplement.

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.

5.1 COMMENTS TO THE APPLICANT

A. All labels and Labeling

1. Add the following statement after sentence 1 of the proposed storage language:

Once removed from the refrigerator, protect from light.

2. The proposed room temperature storage language is not consistent with the tested Version 3 proposed room temperature storage language. Ensure the tested Version 3 proposed room temperature storage language is consistently presented throughout all labels and labeling.
3. Provide a space on the blister label and carton labeling for documentation of the date of initial removal from the refrigerator.
4. Revise sentence 3 of the proposed storage language to state the following:

You should record the date in the XXX space provided when the Humira pen is first removed from the refrigerator.

B. Blister Label

Relocate the (b) (4) statement to the space above the NDC number.

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/s/

TERESA S MCMILLAN
04/11/2012

LUBNA A MERCHANT
04/11/2012

KELLIE A TAYLOR
04/11/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
BLA 125057/S-280

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



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

FACSIMILE TRANSMITTAL SHEET

DATE: December 22, 2014

| | |
|--|---|
| To: Paul Hermes, M.S. Associate Director, Regulatory Affairs | From: Sadaf Nabavian, Pharm.D. Sr. Regulatory Project Manager |
| Company: AbbVie, Inc. | Division of Pulmonary, Allergy, and Rheumatology Products |
| Fax number: 847-935-4079 | Fax number: 301-796-9728 |
| Phone number: 847-937-1585 | Phone number: 301-796-2777 |

Subject: BLA 125057/S-280; FDA labeling Comments

Total no. of pages including cover: 3

Comments: Please confirm receipt. Thanks.

Document to be mailed: YES xNO

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BLA 125057/S-280
Humira
AbbVie Inc.

Dear Mr. Hermes:

Your prior approval labeling supplement submitted on June 26, 2014, for Humira (adalimumab) is currently under review. The FDA proposed recommended labeling revisions are attached. Proposed insertions are underlines and deletions are in strike-out. Please be advised that these labeling changes are not all inclusive and that additional recommendations may be forthcoming as we continue to review this supplement.

Submit revised labeling incorporating the changes outlined in the enclosed labeling via telephone facsimile to 301-796-9728 or email at Sadaf.Nabavian@fda.hhs.gov by noon, Tuesday, December 23, 2014. Your responses will subsequently need to be submitted officially to the sBLA. If there are any questions, contact Sadaf Nabavian, Sr. Regulatory Project Manager, at 301-796-2777.

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/s/

SADAF NABAVIAN
12/22/2014



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

FACSIMILE TRANSMITTAL SHEET

DATE: December 16, 2014

| | |
|--|---|
| To: Paul Hermes, M.S. Associate Director, Regulatory Affairs | From: Sadaf Nabavian, Pharm.D. Sr. Regulatory Project Manager |
| Company: AbbVie, Inc. | Division of Pulmonary, Allergy, and Rheumatology Products |
| Fax number: 847-935-4079 | Fax number: 301-796-9728 |
| Phone number: 847-937-1585 | Phone number: 301-796-2777 |

Subject: BLA 125057/S-280; FDA labeling Comments

Total no. of pages including cover: 3

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BLA 125057/S-280
Humira
AbbVie Inc.

Dear Mr. Hermes:

Your prior approval labeling supplement submitted on June 26, 2014, for Humira (adalimumab) is currently under review. The FDA proposed recommended labeling revisions are attached. Proposed insertions are underlines and deletions are in strike-out and. Please be advised that these labeling changes are not all inclusive and that additional recommendations may be forthcoming as we continue to review this supplement.

Submit revised labeling incorporating the changes outlined in the enclosed labeling via telephone facsimile to 301-796-9728 or email at Sadaf.Nabavian@fda.hhs.gov by COB Thursday, December 18, 2014. Your responses will subsequently need to be submitted officially to the sBLA. If there are any questions, contact Sadaf Nabavian, Sr. Regulatory Project Manager, at 301-796-2777.

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/s/

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12/16/2014



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

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DATE: December 15, 2014

| | |
|--|---|
| To: Paul Hermes, M.S. Associate Director, Regulatory Affairs | From: Sadaf Nabavian, Pharm.D. Sr. Regulatory Project Manager |
| Company: AbbVie, Inc. | Division of Pulmonary, Allergy, and Rheumatology Products |
| Fax number: 847-935-4079 | Fax number: 301-796-9728 |
| Phone number: 847-937-1585 | Phone number: 301-796-2777 |
| Subject: BLA 125057/S-280; FDA Comments | |

Total no. of pages including cover: 3

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BLA 125057/S-280
Humira
AbbVie Inc.

Dear Mr. Hermes:

Your prior approval labeling supplement submitted on June 26, 2014, for Humira (adalimumab) is currently under review and we have the following comments and requests for information.

1. Real-time temperature excursion studies were performed at 25°C for 28 days and at 30°C for 14 days after 24-month storage at 5°C. However, there is a risk that the temperature excursions by patients may exceed these temperature criteria. Additional data demonstrating stability for 14 days at 40°C would help to mitigate this risk. We note that the degradation data for the (b) (4) at 40°C provided in Figure 23 suggest that levels may fail acceptance criteria 75% in less than 10 days when the initial level is approximately 84%. In addition, historical stability data at 40°C show out of specification values for CEX-HPLC results at one month. Provide available data to support the stability of Humira drug product for 14 days at 40°C, including after 24 month storage at 5°C.
2. Provide the adjusted R^2 values for the linear regressions performed on the 5°C and 25°C data for the (b) (4) and the (b) (4).
3. It is concluded in the risk assessment of the storage of Humira drug product at room temperature that all identified potential errors are low to medium risk. Provide the detailed information on the risk assessment that includes the assessment of the consequences of the changes to product quality attributes that are observed. This should include a risk assessment of storage for 14 days at 40°C.

Submit the requested information via email to Sadaf.Nabavian@fda.hhs.gov by COB, Thursday, December 18, 2014, followed by an official submission to the BLA. If there are any questions, contact Sadaf Nabavian, Sr. Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/12.15.2014

Cleared by: LJafari/12.15.2014

Finalized by: SNabavian/12.15.2014

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/s/

SADAF NABAVIAN
12/15/2014



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

FACSIMILE TRANSMITTAL SHEET

DATE: December 4, 2014

| | |
|--|---|
| To: Paul Hermes, M.S. Associate Director, Regulatory Affairs | From: Sadaf Nabavian, Pharm.D. Sr. Regulatory Project Manager |
| Company: AbbVie, Inc. | Division of Pulmonary, Allergy, and Rheumatology Products |
| Fax number: 847-935-4079 | Fax number: 301-796-9728 |
| Phone number: 847-937-1585 | Phone number: 301-796-2777 |
| Subject: BLA 125057/S-280; FDA Comments | |

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BLA 125057/S-280
Humira
AbbVie Inc.

Dear Mr. Hermes:

Your prior approval labeling supplement submitted on June 26, 2014, for Humira (adalimumab) is currently under review and we have the following comments and requests for information. Please be advised that these comments are not all inclusive and that additional recommendations may be forthcoming as we continue to review this supplement.

All Carton Labeling and Institutional Vial Label

1. Ensure the proposed storage option language is adequately added to all carton labeling and to the institutional vial label.

Institutional Vial Label, All Printmat Labeling, All Carton Labeling

2. Provide a space on the institutional vial label, printmat labeling, and all carton labeling for documentation of the date of initial removal from the refrigerator.
3. Submit labels and labeling for all presentations for Agency review once recommendation A(1) and B(1) are implemented. The presentations should include all recently approved container, printmats, and cartons from recently approved supplements (S-355, S-356, S-384, and S-390).

Submit the requested information via email to Sadaf.Nabavian@fda.hhs.gov by COB, Thursday, December 11, 2014, followed by an official submission to the BLA. If there are any questions, contact Sadaf Nabavian, Sr. Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/11.13.2014

Cleared by: LJafari/11.13.201/JMaynard/11.19.2014

Finalized by: SNabavian/11.19.2014

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/s/

SADAF NABAVIAN
12/04/2014

MANDATORY: Send a copy of the consult request form to the Office of Combination Products as follows:
--Originating Center: When the consult request is initiated.
--Consulting Center: When the consult is completed.
Email: combination@fda.gov or FAX: 301-427-1935

For Consulting Center Use Only:

Date Received: _____
Assigned to: _____
Date Assigned: _____
Assigned by: _____

Completed date: _____
Reviewer Initials: _____
Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center: CDRH/ODE/DAGID/GHDB
Division:
Mail Code: HF
Consulting Reviewer Name: LCDR Keith Marin
Building/Room #: Bldg 66, Rm 2567
Phone #: 6-2462
Fax #:
Email Address: Keith.Marin@fda.hhs.gov
RPM/CSO Name and Mail Code: Keith Marin

From (Originating Center):

Center: CDER/OND
Division: DPARP
Mail Code: HF
Requesting Reviewer Name: Dr. Janet Maynard
Building/Room #: Bldg 22, Room 3232
Phone#: 6-2978
Fax #:
Email Address: Janet.Maynard@fda.hhs.gov
RPM/CSO Name and Mail Code: Sadaf.Nabavian/6-2777
Requesting Reviewer's Concurring Supervisor's Name: Ms. Ladan Jafari

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: August 19, 2014

Requested Completion Date: October 20, 2014

Submission/Application Number: BLA 125057/S-280
(Not Barcode Number)

Submission Type: sBLA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: Drug-device combination Drug-biologic combination Device-biologic combination
 Drug-device-biologic combination Not a combination product

Submission Receipt Date: June 26, 2014

Official Submission Due Date: June 26, 2014

Name of Product: Humira (adalimumab)

Name of Firm: AbbVie

Intended Use: Rheumatoid Arthritis

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

This PAS is for changes to the Humira storage instructions to allow a limited room temperature storage option for the Humira prefilled syringes, Humira Pen, and Humira institutional vial presentations. Also, changes are made to the PI, MG, IFU of the pen and prefilled syringe. This is a resubmission to the sBLA in which a CR action was taken on April 27, 2011 (attached). Link is under Supp 280, Seq 304, dated 6/26/2014: <http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea68142c36e>

Documents to be returned to Requesting Reviewer? Yes No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: Consultative Review Collaborative Review

DPARP asked CDRH Device Team if a review was needed for this supplement and CDRH advised that a consult request be officially placed in order for CDRH team review in-depth the impact of the temperature changes on the delivery rate and/or device mechanics (if any). Also, the CR letter and sponsor's proposed labeling update is attached to the consult request for your reference.



COMPLETE RESPONSE

Our STN: BL 125057/280

Abbott Laboratories
Attention: Dr. Tobias Gerwig
Senior Manager, Regulatory Affairs
Dept. PA77, Bld AP30-1 NE
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Dr. Gerwig:

This letter is in regard to the supplement to your biologics license application, dated December 29, 2011, received December 29, 2011, submitted under section 351 of the Public Health Service Act for Humira[®] (adalimumab).

We acknowledge receipt of your amendments dated January 11, 2012 and February 20, 2012.

This supplement was for the modification of storage instructions to allow limited storage of the Humira pre-filled syringe and Humira pen presentations at room temperature, plus a label change to allow storage of Humira up to 25°C for single period of up to 14 days.

We have completed the review of your supplement and have determined that we cannot approve the supplement in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues:

- 1. Storage of biologic products under controlled room temperature conditions is unusual and there is great concern over the ability of patients to consistently maintain the product within the validated storage temperature ($\leq 25^{\circ}\text{C}$). Provide all available information with regard to how controlled room temperature will be maintained and monitored by the patient such as a mechanism to monitor whether storage conditions have exceeded the recommended temperature limit (e.g. a colorimetric temperature indicator). Include information/data which adequately support that control over the controlled room temperature by the patient is sufficient to assure product will be stored within its validated storage temperature.**
- 2. You have not included an updated medication guide that incorporates your proposed changes to the recommended storage conditions consistent with changes noted in the package insert and patient instructions.**

3. Please provide a risk assessment for temperature excursions beyond controlled room temperature while drug product is under patient control.

We reserve comment on the proposed labeling until the supplement is otherwise adequate. If you revise labeling, your response must include updated 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>.

Within one year after the date of this letter, you are required to resubmit or withdraw the application. If you do not take any of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). A resubmission must fully address all the deficiencies listed, and will start a new review cycle. A partial response to this letter may not be reviewed and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss the steps necessary for approval. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry on *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079744.pdf>)

If you have any questions, please contact the Regulatory Project Manager, Andrew Shiber, at (301) 796-4798.

Sincerely,

Patrick Swann, Ph.D. for
Kathleen A. Clouse, Ph.D.
Director
Division of Monoclonal Antibodies
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

PATRICK G SWANN
04/27/2012

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SADAF NABAVIAN
08/19/2014

| | | | | | |
|---|-------------------------------------|--|---|--|--|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION | | REQUEST FOR PATIENT LABELING REVIEW CONSULTATION | | | |
| TO: CDER-DMPP-PatientLabelingTeam | | | FROM: (Name/Title, Office/Division/Phone number of requestor) Sadaf Nabavian, Pharm.D. OND, DPAPR, 301-796-2777 | | |
| REQUEST DATE: August 18, 2014 | | NDA/BLA NO.: BLA 125057/ Supplement 280 | TYPE OF DOCUMENTS: Prior Approval Supplement (PLEASE CHECK OFF BELOW) | | |
| NAME OF DRUG: Humira (adalimumab) | PRIORITY CONSIDERATION: Standard | | CLASSIFICATION OF DRUG: TNF Blocker | DESIRED COMPLETION DATE (Generally 2 Weeks after receiving substantially complete labeling) October 14, 2014 | |
| SPONSOR: AbbVie Inc. | | | PDUFA Date: December 26, 2014 | | |
| TYPE OF LABEL TO REVIEW | | | | | |
| TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> MEDICATION GUIDE <input checked="" type="checkbox"/> INSTRUCTIONS FOR USE(IFU) | | TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input checked="" type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> MANUFACTURING (CMC) SUPPLEMENT <input type="checkbox"/> PLR CONVERSION | | REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION | |
| EDR link to submission: Seq No. 0304, submitted on June 26, 2014: http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea6812c2b4e | | | | | |
| Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format. | | | | | |
| COMMENTS/SPECIAL INSTRUCTIONS: This Prior Approval Supplement is for changes to the Humira storage instructions to allow a limited room temperature storage option for the Humira prefilled syringes, Humira Pen, and Humira institutional vial presentations. Also, changes are made to the prescribing information, medication guide, Instructions for Use of the pen and prefilled syringe. Of note, this is a resubmission to the sBLA in which a CR action was taken on April 27, 2011 (attached to this consult request). DPARP is requesting the review of this supplement. STN 280, Seq 304, submission dated June 26, 2014: http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea68142c36e The PDUFA due date for this supplement is December 26, 2014. Filing/Planning NA Mid-Cycle Meeting: NA Labeling Meetings #1: TBD Labeling Meeting#2: NA Wrap-Up Meeting: NA | | | | | |
| SIGNATURE OF REQUESTER Sadaf Nabavian | | | | | |
| SIGNATURE OF RECEIVER Sadaf Nabavian | | | METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> eMAIL (BLAs Only) <input type="checkbox"/> DARRTS | | |



COMPLETE RESPONSE

Our STN: BL 125057/280

Abbott Laboratories
Attention: Dr. Tobias Gerwig
Senior Manager, Regulatory Affairs
Dept. PA77, Bld AP30-1 NE
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Dr. Gerwig:

This letter is in regard to the supplement to your biologics license application, dated December 29, 2011, received December 29, 2011, submitted under section 351 of the Public Health Service Act for Humira[®] (adalimumab).

We acknowledge receipt of your amendments dated January 11, 2012 and February 20, 2012.

This supplement was for the modification of storage instructions to allow limited storage of the Humira pre-filled syringe and Humira pen presentations at room temperature, plus a label change to allow storage of Humira up to 25°C for single period of up to 14 days.

We have completed the review of your supplement and have determined that we cannot approve the supplement in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues:

- 1. Storage of biologic products under controlled room temperature conditions is unusual and there is great concern over the ability of patients to consistently maintain the product within the validated storage temperature ($\leq 25^{\circ}\text{C}$). Provide all available information with regard to how controlled room temperature will be maintained and monitored by the patient such as a mechanism to monitor whether storage conditions have exceeded the recommended temperature limit (e.g. a colorimetric temperature indicator). Include information/data which adequately support that control over the controlled room temperature by the patient is sufficient to assure product will be stored within its validated storage temperature.**
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3. Please provide a risk assessment for temperature excursions beyond controlled room temperature while drug product is under patient control.

We reserve comment on the proposed labeling until the supplement is otherwise adequate. If you revise labeling, your response must include updated 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>.

Within one year after the date of this letter, you are required to resubmit or withdraw the application. If you do not take any of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). A resubmission must fully address all the deficiencies listed, and will start a new review cycle. A partial response to this letter may not be reviewed and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss the steps necessary for approval. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry on *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079744.pdf>)

If you have any questions, please contact the Regulatory Project Manager, Andrew Shiber, at (301) 796-4798.

Sincerely,

Patrick Swann, Ph.D. for
Kathleen A. Clouse, Ph.D.
Director
Division of Monoclonal Antibodies
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

PATRICK G SWANN
04/27/2012

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/s/

SADAF NABAVIAN
08/19/2014

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|---|---|---|--|--|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION | | REQUEST FOR CONSULTATION | | |
| TO (Division/Office): Mail: OSE | | FROM: Sadaf Nabavian, 301-796-2777 OND/DPARP | | |
| DATE August 18, 2014 | IND NO. | NDA NO. BLA 125057/ S-280 | TYPE OF DOCUMENT Prior Approval Supplement | DATE OF DOCUMENT June 26, 2014 |
| NAME OF DRUG Humira (adalimumab) | PRIORITY CONSIDERATION Standard | CLASSIFICATION OF DRUG TNF blocker | DESIRED COMPLETION DATE October 14, 2014 | |
| NAME OF FIRM: AbbVie Inc. | | | | |
| 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 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 type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW): | | | | |
| 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 checked="" 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: This Prior Approval Supplement is for changes to the Humira storage instructions to allow a limited room temperature storage option for the Humira prefilled syringes, Humira Pen, and Humira institutional vial presentations. Also, changes are made to the prescribing information, medication guide, Instructions for Use of the pen and prefilled syringe. Of note, this is a resubmission to the sBLA in which a CR action was taken on April 27, 2011 (attached to this consult request). DPARP is requesting the review of this supplement. Also, see the link below under STN 280, Seq 304, submission dated June 26, 2014: http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea68142c36e > The PDUFA due date for this supplement is December 26, 2014. | | | | |
| SIGNATURE OF REQUESTER Sadaf Nabavia/6-2777 | | METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND | | |
| SIGNATURE OF RECEIVER | | SIGNATURE OF DELIVERER | | |



COMPLETE RESPONSE

Our STN: BL 125057/280

Abbott Laboratories
Attention: Dr. Tobias Gerwig
Senior Manager, Regulatory Affairs
Dept. PA77, Bld AP30-1 NE
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Dr. Gerwig:

This letter is in regard to the supplement to your biologics license application, dated December 29, 2011, received December 29, 2011, submitted under section 351 of the Public Health Service Act for Humira[®] (adalimumab).

We acknowledge receipt of your amendments dated January 11, 2012 and February 20, 2012.

This supplement was for the modification of storage instructions to allow limited storage of the Humira pre-filled syringe and Humira pen presentations at room temperature, plus a label change to allow storage of Humira up to 25°C for single period of up to 14 days.

We have completed the review of your supplement and have determined that we cannot approve the supplement in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues:

- 1. Storage of biologic products under controlled room temperature conditions is unusual and there is great concern over the ability of patients to consistently maintain the product within the validated storage temperature ($\leq 25^{\circ}\text{C}$). Provide all available information with regard to how controlled room temperature will be maintained and monitored by the patient such as a mechanism to monitor whether storage conditions have exceeded the recommended temperature limit (e.g. a colorimetric temperature indicator). Include information/data which adequately support that control over the controlled room temperature by the patient is sufficient to assure product will be stored within its validated storage temperature.**
- 2. You have not included an updated medication guide that incorporates your proposed changes to the recommended storage conditions consistent with changes noted in the package insert and patient instructions.**

3. Please provide a risk assessment for temperature excursions beyond controlled room temperature while drug product is under patient control.

We reserve comment on the proposed labeling until the supplement is otherwise adequate. If you revise labeling, your response must include updated 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>.

Within one year after the date of this letter, you are required to resubmit or withdraw the application. If you do not take any of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). A resubmission must fully address all the deficiencies listed, and will start a new review cycle. A partial response to this letter may not be reviewed and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss the steps necessary for approval. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry on *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079744.pdf>)

If you have any questions, please contact the Regulatory Project Manager, Andrew Shiber, at (301) 796-4798.

Sincerely,

Patrick Swann, Ph.D. for
Kathleen A. Clouse, Ph.D.
Director
Division of Monoclonal Antibodies
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

PATRICK G SWANN
04/27/2012

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following this page

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/s/

SADAF NABAVIAN
08/19/2014

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|---|--|--|--|--|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION | | REQUEST FOR CONSULTATION | | |
| TO (Office/Division): OBP | | FROM (Name, Office/Division, and Phone Number of Requestor): Sadaf Nabavian, OND, DPARP, 301-796-2777 | | |
| DATE July 18, 2014 | IND NO. | NDA NO. sBLA 125057/S-280 | TYPE OF DOCUMENT Prior Approval Supplement | DATE OF DOCUMENT June 26, 2014 |
| NAME OF DRUG Humira (adalimumab) | PRIORITY CONSIDERATION No | CLASSIFICATION OF DRUG TNF Blocker | DESIRED COMPLETION DATE September 26, 2014 | |
| NAME OF FIRM: AbbVie | | | | |
| REASON FOR REQUEST | | | | |
| I. GENERAL | | | | |
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER | | |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING | | |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION | | |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE | | |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW | | |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): | | |
| <input type="checkbox"/> MEETING PLANNED BY | | | | |
| II. BIOMETRICS | | | | |
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW | | | |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY | | | |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS | | | |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): | | | |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | | | | |
| III. BIOPHARMACEUTICS | | | | |
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE | | | |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS | | | |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST | | | |
| IV. DRUG SAFETY | | | | |
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY | | | |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE | | | |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS | | | |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | | | | |
| V. SCIENTIFIC INVESTIGATIONS | | | | |
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL | | | |
| COMMENTS / SPECIAL INSTRUCTIONS: This Prior Approval Supplement is for changes to the Humira storage instructions to allow a limited room temperature storage option for the Humira prefilled syringes, Humira Pen, and Humira institutional vial presentations. Also, changes are made to the prescribing information, medication guide, Instructions for Use of the pen and prefilled syringe. Of note, this is a resubmission to the sBLA in which a CR action was taken on April 27, 2011 (attached to this consult request). DPARP is requesting the review of this supplement. STN 280, Seq 304, submission dated June 26, 2014: http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea68142c36e > The PDUFA due date for this supplement is December 26, 2014. | | | | |
| SIGNATURE OF REQUESTOR Sadaf Nabavian | | METHOD OF DELIVERY (Check all that apply) <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND | | |
| PRINTED NAME AND SIGNATURE OF RECEIVER | | NAME AND SIGNATURE OF DELIVERER | | |



COMPLETE RESPONSE

Our STN: BL 125057/280

Abbott Laboratories
Attention: Dr. Tobias Gerwig
Senior Manager, Regulatory Affairs
Dept. PA77, Bld AP30-1 NE
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Dr. Gerwig:

This letter is in regard to the supplement to your biologics license application, dated December 29, 2011, received December 29, 2011, submitted under section 351 of the Public Health Service Act for Humira[®] (adalimumab).

We acknowledge receipt of your amendments dated January 11, 2012 and February 20, 2012.

This supplement was for the modification of storage instructions to allow limited storage of the Humira pre-filled syringe and Humira pen presentations at room temperature, plus a label change to allow storage of Humira up to 25°C for single period of up to 14 days.

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- 2. You have not included an updated medication guide that incorporates your proposed changes to the recommended storage conditions consistent with changes noted in the package insert and patient instructions.**

3. Please provide a risk assessment for temperature excursions beyond controlled room temperature while drug product is under patient control.

We reserve comment on the proposed labeling until the supplement is otherwise adequate. If you revise labeling, your response must include updated 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>.

Within one year after the date of this letter, you are required to resubmit or withdraw the application. If you do not take any of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). A resubmission must fully address all the deficiencies listed, and will start a new review cycle. A partial response to this letter may not be reviewed and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss the steps necessary for approval. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry on *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079744.pdf>)

If you have any questions, please contact the Regulatory Project Manager, Andrew Shiber, at (301) 796-4798.

Sincerely,

Patrick Swann, Ph.D. for
Kathleen A. Clouse, Ph.D.
Director
Division of Monoclonal Antibodies
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

PATRICK G SWANN
04/27/2012

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/s/

SADAF NABAVIAN
07/18/2014



BLA 125057/S-280

**MEETING REQUEST-
WRITTEN RESPONSES**

AbbVie Inc.
1 North Waukegan Road
Department PA77, Building AP30
North Chicago, IL 60064

Attention: Gresham Weatherly
Director, Regulatory Affairs

Dear Mr. Weatherly:

Please refer to your supplemental Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for Humira (adalimumab).

We also refer to your September 18, 2013, containing a Type C meeting request. The purpose of the requested meeting was to discuss our comments stated in the Complete Response letter communicated to you on April 27, 2012, regarding the proposed room temperature storage option for the Humira Pre-Filled Syringe and Pen presentation.

Further reference is made to our Meeting Granted letter dated October 25, 2013, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your September 18, 2013, meeting request.

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Written Response



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: Type C
Meeting Category: End-of-Review Meeting
Application Number: BLA 125057/S-280
Product Name: Humira (adalimumab)
Indication: RA, JIA, PsA, AS, CD, UC, Ps
Applicant Name: AbbVie
Regulatory Pathway: §351 of the Public Health Service Act

1.0 BACKGROUND

This document provides written responses to Abbvie's questions regarding the comments stated in the Complete Response letter communicated on April 27, 2012, for the proposed room temperature storage option for Humira pre-filled syringe and pen presentation. The Division granted the meeting as written responses and the background materials were received by the Agency on October 30, 2013.

2. QUESTIONS AND RESPONSES

Question 1:

AbbVie contends that risk assessment, label comprehension testing, stability assessment, and the precedence for biologics demonstrate that a patient can safely use Humira under the proposed room temperature storage condition. Does the Agency agree?

FDA Response:

Stability data and updated labeling should be sufficient to support the proposed room temperature storage condition. We do not think label comprehension or human data are needed.

Of note, the stability of Humira under the proposed room temperature storage conditions will require a review of the available data for all of the assays used to monitor stability. Provide the stability data to support all impacted presentations under the proposed storage condition of Humira up to 25°C (77°F) for a single period of up to 14 days and excursions beyond 25°C. Adequacy of the data will be a review issue.

Question 2:

Can the Agency provide further comments on the steps necessary for approval of the proposed room temperature storage option for Humira?

FDA Response:

See our response to Question 1.

Question 3:

Could the Agency confirm receipt of the proposed Medication Guide, which was part of the eCTD submission provided to the FDA on 29 December 2011?

FDA Response:

We confirm receipt of your proposed Medication Guide submitted on December 29, 2011. However, when responding to the complete response action letter dated April 27, 2012, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert.

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/s/

SADAF NABAVIAN
11/26/2013



BLA 125057/S-280

**MEETING REQUEST GRANTED
WRITTEN RESPONSES ONLY**

AbbVie Inc.
1 North Waukegan Road
North Chicago, IL 60064

Attention: Gresham Weatherly
Director, Regulatory Affairs

Dear Mr. Weatherly:

Please refer to your supplemental Biologic License Application (sBLA) submitted under section 351(a) of the Public Health Service Act for Humira (adalimumab).

We also refer to your September 18, 2013, correspondence requesting a meeting to discuss our comments stated in the Complete Response letter communicated to you on April 27, 2012, regarding the proposed room temperature storage option for the Humira Pre-Filled Syringe and Pen presentation. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a Type C meeting.

We have determined that written responses to your questions would be the most appropriate means for responding to the meeting request. Therefore, a meeting will not be scheduled. Our goal date for providing our written responses is November 29, 2013.

Submit background information (three paper copies or one electronic copy to the application and 14 paper desk copies to the RPM) as soon as possible but no later than 4 weeks prior to our goal date for sending written responses (as stated above) for our review and response. If the materials presented in the background package are inadequate to answer the questions or if we do not receive the package by November 01, 2013, we may cancel the agreement to provide written responses. If we cancel the agreement to provide written responses, a new meeting request will be required.

Submit 14 desk copies to the following address:

Sadaf Nabavian
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3306
10903 New Hampshire Avenue
Silver Spring, Maryland

*Use zip code **20903** if shipping via United States Postal Service (USPS).*

*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

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

Sincerely,

{See appended electronic signature page}

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

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/s/

SADAF NABAVIAN
10/25/2013



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

FACSIMILE TRANSMITTAL SHEET

DATE: May 16, 2012

| | |
|---|--|
| To: Ray Votzmeyer | From: Ladan Jafari |
| Company: Abbott | Division of Pulmonary and Allergy Drug Products |
| Email: Ray C Votzmeyer [Raymond.C.Votzmeyer@abbott.com] | Fax number: 301-796-9728 |
| Phone number: 847-938-9490 | Phone number: 301-796-2300 |

Subject: BLA 125057, Prior Approval Supplement 280

Total no. of pages including cover: 3

Comments: Labeling comments for Humira supplement 280

Document to be mailed: YES XNO

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, or a person authorized to deliver this document to 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 have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

Dear Mr. Votzmeyer:

Reference is made to your submission dated December 29, 2011, and the Complete Response Action letter issued on April 27, 2012.

We are providing the following preliminary labeling recommendations and request that you also address these comments when you resubmit the above supplement. Please note that we may have additional labeling recommendations after we receive the response to this supplement.

1. The following pertain to the Pediatric Patient formulation-Syringe (20 mg/0.4 mL)
 - a. To reduce crowding, improve legibility, and create space, remove the following items from the immediate container label:



* See Recommended format below

2. The following comments pertain to the Adult preparation Pen and Syringe label (40 mg/0.8 mL)
 - a. To reduce crowding, improve legibility, and create space remove the following items from the immediate container label:

(b) (4)



* See Recommended format below

*Recommended format:

(b) (4)



I may be reached at 301-796-1231 for any questions.

Ladan Jafari
Chief, Project Management Staff

BLA 125057/280

Page 4

Drafted by: LJ/5-14-12

Initialed by: Maynard/5-14-2012
Yim/5-15-2012

Filename: S280 labeling comments.doc

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/s/

LADAN JAFARI
05/16/2012

Cordoba-Rodriguez, Ruth; Rains, Kimberly E; Park, Jun; Hulett, Melissa; Williams, Sharon; Chi, Bo; Rashid, Nichelle E; Mcmillan, Teresa; Merchant, Lubna; CDER WO 1537 conf rm Bldg21 - AR; Tobenkin, Anne

Mid Cycle Meeting for STN 125057/280

Tcon

Fri 3/16/2012

10:30AM - 11:00AM

Phone #: [REDACTED] (b) (4)

Participant Passcode: [REDACTED] (b) (4)

Good Day Review Team,

OBP has received a PAS from Abbott:

Date of Submission: 29-Dec-11
CBER Receipt Date: 29-Dec-11
DCC Login ID: [REDACTED] (b) (4)
Product: Adalimumab
STN: 125057/280
Action Due Date: **April 27, 2012**

Short Summary: For the modification of storage instructions to allow limited storage of the Humira pre-filled syringe and Humira pen presentations at room temperature, plus a label change to allow storage of Humira up to 25°C for single period of up to 14 days can be supported.

please see the supplement below under sequence: 0111
<<http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea680f6dee8>>

Thank You for Your Help

Andrew

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/s/

ANDREW J SHIBER
04/11/2012

Sent: Thu 3/8/2012 3:48 PM

From: Pohlhaus, Timothy

To: Chi, Bo

Final TB-EER response - Abbott PAS STN125057/280

The Division of Good Manufacturing Practice Assessment has completed its review and evaluation of the TB-EER for STN 125057/280. Please see below for individual site compliance statuses. There are no pending or ongoing compliance actions that prevent approval of this supplement.

Timothy J. Pohlhaus, Ph.D.

Interdisciplinary Scientist, Chemist

Food and Drug Administration

CDER/OC/OMPQ

10903 New Hampshire Avenue

Building 51, Room 1333

Silver Spring, MD 20993

Phone - (301) 796-5224

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/s/

ANDREW J SHIBER
04/11/2012

From: Chi, Bo
Sent: Tuesday, March 06, 2012 2:49 PM
To: CDER-TB-EER
Subject: Final TB-EER for Abbott's PAS STN125057/280

Hi,

Please provide a TB-EER for Abbott's PAS STN125057/280 for the facilities listed below: For the modification of storage instructions to allow limited storage of the Humira pre-filled syringe and Humira pen presentations at room temperature, plus a label change to allow storage of Humira up to 25°C for single period of up to 14 days can be supported. The PDUFA date is 4/29/2012.

The stability tests are conducted in these facilities:
Abbott Biotechnology Ltd.
Road No. 2, Km. 59.2
Barceloneta,
Puerto Rico 00617
FEI: 3004620772

Inspected by SJN-DO March 18-29, 2011 and classified VAI. This was a routine GMP surveillance inspection. The CBI and TRP profiles are currently acceptable.

Abbott GmbH & Co. KG
Knollstrasse
Ludwigshafen,
Germany 67061
FEI: 3002807401

(b) (4)

Inspected by IOG December 11-17, 2009 and classified VAI. The was a PAI and GMP inspection. The CTL profile was updated and is acceptable.

Thanks,
Bo

Thanks

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/s/

ANDREW J SHIBER
04/11/2012

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR BLA/NDA Supplements (OBP & DMPQ)**

BLA/NDA Number: **125057/280** Applicant: **Abbott Laboratories** Stamp Date: **29-Dec-11**
 Established/Proper Name: **Humira®/adalimumab** BLA/NDA Type: **BLA**

| | |
|---|---|
| Brief description of the change: | For the modification of storage instructions to allow limited storage of the Humira pre-filled syringe and Humira pen presentations at room temperature, plus a label change to allow storage of Humira up to 25°C for single period of up to 14 days can be supported. |
| Reviewer: | Jun Park, Bo Chi |
| Office/Division: | OBP/DMA |

On **initial** overview of the BLA/NDA **supplement** for filing:

The following was submitted in support of the change (check all that apply):

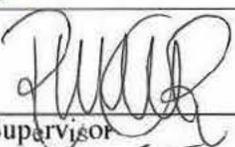
| | |
|-------------------------------------|---|
| <input checked="" type="checkbox"/> | A detailed description of the proposed change |
| <input checked="" type="checkbox"/> | Identification of the product(s) involved |
| <input type="checkbox"/> | A description of the manufacturing site(s) or area(s) affected |
| <input checked="" type="checkbox"/> | A description of the methods used and studies performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product |
| <input checked="" type="checkbox"/> | The data derived from such studies |
| <input checked="" type="checkbox"/> | Relevant validation protocols and data |
| <input checked="" type="checkbox"/> | A reference list of relevant standard operating procedures (SOP's) |

The following deficiencies were identified (identify those that are potential filing issues):

IS THE PRODUCT QUALITY SECTION OF THE SUPPLEMENT FILEABLE? **Yes** No

If the supplement is not fileable from the product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Product Quality Reviewer:  Date: 2-22-2012
 Branch Chief/Team Leader/Supervisor:  Date: 2-22-2012

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/s/

JUN T PARK
03/01/2012

RUTH V CORDOBA RODRIGUE
03/06/2012

| | | | | |
|---|------------------------|---|---|--|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION | | REQUEST FOR CONSULTATION | | |
| TO (Division/Office): CDER/OSE/PLT | | FROM (Division/Office) Kimberly Rains, Pharm.D. CDER/OPS/OBP | | |
| DATE: February 24, 2012 | NDA NO. | STN NO. 125057/280 | TYPE OF DOCUMENT: Labeling | DATE OF DOCUMENTS: December 29, 2011 |
| NAME OF DRUG Humira (adalimumab) | PRIORITY CONSIDERATION | | CLASSIFICATION OF DRUG: Rheumatoid Arthritis | DESIRED COMPLETION DATE: April 1, 2012 |
| NAME OF FIRM: Abbott Laboratories | | | | |
| REASON FOR REQUEST | | | | |
| I. GENERAL | | | | |
| <u>NEW PROTOCOL</u> PROGRESS REPORT NEW CORRESPONDENCE <u>DRUG ADVERTISING</u> ADVERSE REACTION REPORT xx MANUFACTURING CHANGE/ADDITION MEETING PLANNED BY | | PRE--NDA MEETING END OF PHASE II MEETING RESUBMISSION <u>SAFETY</u> PAPER NDA CONTROL SUPPLEMENT | RESPONSE TO DEFICIENCY LETTER FINAL PRINTED LABELING <input checked="" type="checkbox"/> LABELING REVISION ORIGINAL NEW CORRESPONDENCE FORMULATIVE REVIEW xx OTHER (SPECIFY BELOW): | |
| COMMENTS/SPECIAL INSTRUCTIONS: This submission contains a label comprehension study, carton and container labels, and changes to the PI. http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea680f6dee8 Attached link under sequence 111 & 124 for the submissions. | | | | |
| SIGNATURE OF REQUESTER Andrew Shiber CDER/OPS/OBP | | METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> EMAIL SCAN MAIL FACSIMILE | | |
| SIGNATURE OF RECEIVER | | SIGNATURE OF DELIVERER | | |

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/s/

ANDREW J SHIBER
02/24/2012
PLT Consult Request

| | | | | |
|--|------------------------|---|---|---|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION | | REQUEST FOR CONSULTATION | | |
| TO (Division/Office): CDER/OSE/DMEPA | | FROM (Division/Office) Kimberly Rains, Pharm.D. CDER/OPS/OBP | | |
| DATE: February 17, 2012 | NDA NO. | STN NO. 125057/280 | TYPE OF DOCUMENT: Labeling | DATE OF DOCUMENTS: December 29, 2011 |
| NAME OF DRUG Humira (adalimumab) | PRIORITY CONSIDERATION | CLASSIFICATION OF DRUG: Rheumatoid Arthritis | DESIRED COMPLETION DATE: April 1, 2012 | |
| NAME OF FIRM: Abbott Laboratories | | | | |
| REASON FOR REQUEST | | | | |
| I. GENERAL | | | | |
| <u>NEW PROTOCOL</u> PROGRESS REPORT NEW CORRESPONDENCE <u>DRUG ADVERTISING</u> ADVERSE REACTION REPORT XX MANUFACTURING CHANGE/ADDITION MEETING PLANNED BY | | PRE--NDA MEETING END OF PHASE II MEETING RESUBMISSION <u>SAFETY</u> PAPER NDA CONTROL SUPPLEMENT | RESPONSE TO DEFICIENCY LETTER FINAL PRINTED LABELING <input checked="" type="checkbox"/> LABELING REVISION ORIGINAL NEW CORRESPONDENCE FORMULATIVE REVIEW XX OTHER (SPECIFY BELOW): | |
| COMMENTS/SPECIAL INSTRUCTIONS: This submission contains a label comprehension study, carton and container labels, and changes to the PI. http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea680f6dee8 Attached link under sequence 111 for the submission. | | | | |
| SIGNATURE OF REQUESTER Andrew Shiber CDER/OPS/OBP | | METHOD OF DELIVERY (Check one) XX EMAIL SCAN MAIL FACSIMILE | | |
| SIGNATURE OF RECEIVER | | SIGNATURE OF DELIVERER | | |

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/s/

ANDREW J SHIBER
02/22/2012