HULIO- adalimumab
Mylan Specialty L.P.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use HULIO safely and effectively. See full prescribing information for HULIO.

HULIO® (adalimumab-fkjp) injection, for subcutaneous use
Initial U.S. Approval: 2020

HULIO® (adalimumab-fkjp) is biosimilar* to HUMIRA (adalimumab)

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 HULIO 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 HULIO.**
- **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 adalimumab products.**
- **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 adalimumab products.**

RECENT MAJOR CHANGES

Indications and Usage, Juvenile Idiopathic Arthritis (1.2) 07/2022
Indications and Usage, Crohn's Disease (1.5) 07/2022
Indications and Usage, Hidradenitis Suppurativa (1.8) 03/2023
Indications and Usage, Uveitis (1.9) 08/2023
Dosage and Administration, Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis (2.1) 07/2022
Dosage and Administration, Juvenile Idiopathic Arthritis (2.2) 07/2022
Dosage and Administration, Crohn's Disease (2.3) 07/2022
Dosage and Administration, Hidradenitis Suppurativa (2.6) 03/2023

INDICATIONS AND USAGE

HULIO is a tumor necrosis factor (TNF) blocker indicated for:

- **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.
- **Crohn's Disease (CD) (1.5):** treatment of moderately to severely active Crohn's disease in adults and pediatric patients 6 years of age and older.

- **Ulcerative Colitis (UC) (1.6):** treatment of moderately to severely active ulcerative colitis in adult patients.
- Limitations of Use: Effectiveness has not been established in patients who have lost response to or were intolerant to TNF blockers.
- **Plaque Psoriasis (Ps) (1.7):** 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.
- **Hidradenitis Suppurativa (HS) (1.8):** treatment of moderate to severe hidradenitis suppurativa in adult patients.
- **Uveitis (UV) (1.9):** treatment of non-infectious intermediate, posterior, and panuveitis in adult patients.

DOSAGE AND ADMINISTRATION

- Administer by subcutaneous injection (2)

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

- *Adults:* 40 mg every other week.
    - Some patients with RA not receiving methotrexate may benefit from increasing the dosage to 40 mg every week or 80 mg every other week.

Juvenile Idiopathic Arthritis (2.2):

Pediatric Weight 2 Years of Age and Older	Recommended Dosage
15 kg (33 lbs) to less than 30 kg (66 lbs)	20 mg every other week
30 kg (66 lbs) and greater	40 mg every other week

Crohn's Disease (2.3):

- *Adults:* 160 mg on Day 1 (given in one day or split over two consecutive days); 80 mg on Day 15; and 40 mg every other week starting on Day 29.
- *Pediatric Patients 6 Years of Age and Older:*

Pediatric Weight	Recommended Dosage	
	Days 1 and 15	Starting on Day 29
17 kg (37 lbs) to less than 40 kg (88 lbs)	Day 1: 80 mg Day 15: 40 mg	20 mg every other week
40 kg (88 lbs) and greater	Day 1: 160 mg (single dose or split over two consecutive days) Day 15: 80 mg	40 mg every other week

Ulcerative Colitis (2.4):

- *Adults:* 160 mg on Day 1 (given in one day or split over two consecutive days), 80 mg on Day 15 and 40 mg every other week starting on Day 29. Discontinue in patients without evidence of clinical remission by eight weeks (Day 57).

Plaque Psoriasis or Adult Uveitis (2.5):

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

Hidradenitis Suppurativa (2.6):

- *Adults:*
    - Day 1: 160 mg (given in one day or split over two consecutive days)
    - Day 15: 80 mg
    - Day 29 and subsequent doses: 40 mg every week or 80 mg every other week

DOSAGE FORMS AND STRENGTHS

- Injection: 40 mg/0.8 mL in a single-dose prefilled pen (HULIO Pen) (3)
- Injection: 40 mg/0.8 mL in a single-dose prefilled plastic syringe (3)
- Injection: 20 mg/0.4 mL in a single-dose prefilled plastic syringe (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- *Serious infections:* Do not start HULIO during an active infection. If an infection develops, monitor carefully, and stop HULIO if infection becomes serious. (5.1)
- *Invasive fungal infections:* For patients who develop a systemic illness on HULIO, 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 adalimumab-treated patients than in controls. (5.2)
- *Anaphylaxis or serious hypersensitivity reactions* may occur. (5.3)
- *Hepatitis B virus reactivation:* Monitor HBV carriers during and several months after therapy. If reactivation occurs, stop HULIO 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 HULIO. (5.6)
- *Heart failure:* Worsening or new onset, may occur. (5.8)
- *Lupus-like syndrome:* Stop HULIO if syndrome develops. (5.9)

ADVERSE REACTIONS

Most common adverse reactions (>10%) are: infections (e.g. upper respiratory, sinusitis), injection site reactions, headache and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Mylan at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

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

*Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product.

Biosimilarity of HULIO has been demonstrated for the condition(s) of use (e.g. indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2023

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FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS and MALIGNANCY

SERIOUS INFECTIONS

Patients treated with adalimumab products including HULIO 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 HULIO 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 HULIO use and during therapy. Initiate treatment for latent TB prior to HULIO 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 HULIO 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 HULIO, 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 adalimumab products *[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 adalimumab products. 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

HULIO 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. HULIO can be used alone or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs).

1.2 Juvenile Idiopathic Arthritis

HULIO is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. HULIO can be used alone or in combination with methotrexate.

1.3 Psoriatic Arthritis

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

1.4 Ankylosing Spondylitis

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

1.5 Crohn’s Disease

HULIO is indicated for the treatment of moderately to severely active Crohn’s disease in adults and pediatric patients 6 years of age and older.

1.6 Ulcerative Colitis

HULIO is indicated for the treatment of moderately to severely active ulcerative colitis in adult patients.

Limitations of Use

The effectiveness of adalimumab products has not been established in patients who have lost response to or were intolerant to TNF blockers *[see Clinical Studies (14.7, 14.8)]*.

1.7 Plaque Psoriasis

HULIO 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. HULIO should only be

administered to patients who will be closely monitored and have regular follow-up visits with a physician *[see Warnings and Precautions (5)]*.

1.8 Hidradenitis Suppurativa

HULIO is indicated for the treatment of moderate to severe hidradenitis suppurativa in adult patients.

1.9 Uveitis

HULIO is indicated for the treatment of non-infectious intermediate, posterior, and panuveitis in adult patients.

2 DOSAGE AND ADMINISTRATION

2.1 Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis

The recommended subcutaneous dosage of HULIO 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 HULIO. In the treatment of RA, some patients not taking concomitant MTX may derive additional benefit from increasing the dosage of HULIO to 40 mg every week or 80 mg every other week.

2.2 Juvenile Idiopathic Arthritis

The recommended subcutaneous dosage of HULIO 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 HULIO.

Pediatric Weight (2 Years of Age and older)	**Recommended Dosage**
15 kg (33 lbs) to less than 30 kg (66 lbs)	20 mg every other week
30 kg (66 lbs) and greater	40 mg every other week

There is no dosage form for HULIO that allows weight-based dosing for pediatric patients below 15 kg.

Adalimumab products have 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 Crohn’s Disease

Adults

The recommended subcutaneous dosage of HULIO for adult patients with Crohn’s disease (CD) is 160 mg initially on Day 1 (given in one day or split over two consecutive days), followed by 80 mg two weeks later (Day 15). Two weeks later (Day 29) begin a dosage of 40 mg every other week. Aminosalicylates and/or corticosteroids may be

continued during treatment with HULIO. Azathioprine, 6-mercaptopurine (6-MP) *[see Warnings and Precautions (5.2)]* or MTX may be continued during treatment with HULIO if necessary.

Pediatrics

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

Pediatric Weight	**Recommended Dosage**	
	Days 1 through 15	**Starting on Day 29**
17 kg (37 lbs) to less than 40 kg (88 lbs)	Day 1: 80 mg Day 15: 40 mg	20 mg every other week
40 kg (88 lbs) and greater	Day 1: 160 mg (single dose or split over two consecutive days) Day 15: 80 mg	40 mg every other week

2.4 Ulcerative Colitis

Adults

The recommended subcutaneous dosage of HULIO for adult patients with ulcerative colitis is 160 mg initially on Day 1 (given in one day or split over two consecutive days), followed by 80 mg two weeks later (Day 15). Two weeks later (Day 29) continue with a dosage of 40 mg every other week.

Discontinue HULIO in adult patients without evidence of clinical remission by eight weeks (Day 57) of therapy. Aminosalicylates and/or corticosteroids may be continued during treatment with HULIO. Azathioprine and 6-mercaptopurine (6-MP) *[see Warnings and Precautions (5.2)]* may be continued during treatment with HULIO if necessary.

2.5 Plaque Psoriasis or Adult Uveitis

The recommended subcutaneous dosage of HULIO for adult patients with plaque psoriasis (Ps) or Uveitis (UV) 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 adalimumab products in moderate to severe chronic Ps beyond one year has not been evaluated in controlled clinical studies.

2.6 Hidradenitis Suppurativa

Adults

The recommended subcutaneous dosage of HULIO for adult patients with hidradenitis suppurativa (HS) is an initial dose of 160 mg (given in one day or split over two consecutive days), followed by 80 mg two weeks later (Day 15). Begin 40 mg weekly or 80 mg every other week dosing two weeks later (Day 29).

2.7 Monitoring to Assess Safety

Prior to initiating HULIO 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

HULIO is intended for use under the guidance and supervision of a physician. A patient may self-inject HULIO or a caregiver may inject HULIO using either the HULIO 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.

HULIO can be taken out of the refrigerator for 15 to 30 minutes before injecting to allow the liquid to come to room temperature. Do not remove the cap or cover while allowing it to reach room temperature. Carefully inspect the solution in the HULIO Pen or prefilled syringe for particulate matter and discoloration prior to subcutaneous administration. If particulates and discolorations are noted, do not use the product. HULIO does not contain preservatives; therefore, discard unused portions of drug remaining from the syringe.

Instruct patients using the HULIO 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.

If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regular scheduled time.

3 DOSAGE FORMS AND STRENGTHS

HULIO is a clear to slightly opalescent, colorless to pale brownish-yellow solution available as:

- **Pen** (HULIO Pen)
  Injection: 40 mg/0.8 mL in a single-dose pen.
- **Prefilled Syringe**
  Injection: 40 mg/0.8 mL in a single-dose prefilled plastic syringe.
  Injection: 20 mg/0.4 mL in a single-dose prefilled plastic syringe.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Patients treated with adalimumab products including HULIO are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death. 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 HULIO 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 HULIO should not be initiated in patients with an active infection, including localized infections. Patients 65 years of age and older, 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 adalimumab products, 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 HULIO 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 HULIO, 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 HULIO 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 adalimumab products. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating antituberculosis therapy is appropriate for an individual patient.

Strongly consider tuberculosis in the differential diagnosis in patients who develop a new infection during HULIO 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 HULIO, 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 HULIO.

Discontinue HULIO if a patient develops a serious infection or sepsis. For a patient who develops a new infection during treatment with HULIO, 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 HULIO 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 adalimumab products, more cases of malignancies have been observed among TNF-blocker-treated adult patients compared to control-treated adult patients. During the controlled portions of 39 global adalimumab clinical trials in adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn’s disease (CD), ulcerative colitis (UC), plaque psoriasis (Ps), hidradenitis suppurativa (HS) and uveitis (UV), malignancies, other than non-melanoma (basal cell and squamous cell) skin cancer, were observed at a rate (95% confidence interval) of 0.7 (0.48, 1.03) per 100 patient-years among 7973 adalimumab-treated patients versus a rate of 0.7 (0.41, 1.17) per 100 patient-years among 4848 control-treated patients (median duration of treatment of 4 months for adalimumab-treated patients and 4 months for control-treated patients). In 52 global controlled and uncontrolled clinical trials of adalimumab in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the most frequently observed malignancies, other than lymphoma and NMSC, were breast, colon, prostate, lung, and melanoma. The malignancies in adalimumab-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 39 global adalimumab clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the rate (95% confidence interval) of NMSC was 0.8 (0.52, 1.09) per 100 patient-years among adalimumab-treated patients and 0.2 (0.10, 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 HULIO.

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 39 global adalimumab clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, 2 lymphomas occurred among 7973 adalimumab-treated patients versus 1 among 4848 control-treated patients. In 52 global controlled and uncontrolled clinical trials of adalimumab in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV with a median duration of approximately 0.7 years, including 24,605 patients and over 40,215 patient-years of adalimumab, 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 adalimumab 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 ≤ 18 years of age), of which HULIO is a member. 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 adalimumab products. 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 HULIO should be carefully considered.

5.3 Hypersensitivity Reactions

Anaphylaxis and angioneurotic edema have been reported following administration of adalimumab products. If an anaphylactic or other serious allergic reaction occurs, immediately discontinue administration of HULIO and institute appropriate therapy. In clinical trials of adalimumab, hypersensitivity reactions (e.g., 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 HULIO, 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 HULIO 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 HULIO therapy in this situation and monitor patients closely.

5.5 Neurologic Reactions

Use of TNF blocking agents, including adalimumab products, 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 HULIO in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of HULIO should be considered if any of these disorders develop. There is a known association between intermediate uveitis and central 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 adalimumab products. The causal relationship of these reports to adalimumab products 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 HULIO. Consider discontinuation of HULIO therapy in patients with confirmed significant hematologic abnormalities.

5.7 Increased Risk of Infection when Used 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 HULIO 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 adalimumab products. Adalimumab products have 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 HULIO in patients who have heart failure and monitor them carefully.

5.9 Autoimmunity

Treatment with adalimumab products 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 HULIO, 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 adalimumab and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with adalimumab. Similar proportions of patients developed protective levels of anti-influenza antibodies between adalimumab and placebo treatment groups; however, titers in aggregate to influenza antigens were moderately lower in patients receiving adalimumab. The clinical significance of this is unknown. Patients on HULIO may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving adalimumab products.

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 HULIO therapy. Patients on HULIO may receive concurrent vaccinations, except for live vaccines.

The safety of administering live or live-attenuated vaccines in infants exposed to adalimumab products *in utero* is unknown. Risks and benefits should be considered prior to vaccinating (live or live attenuated) exposed infants *[see Use in Specific Populations (8.1, 8.4)].*

5.11 Increased Risk of Infection When Used 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 HULIO is not recommended *[see Drug Interactions (7.2)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Serious Infections *[see Warnings and Precautions (5.1)]*
- Malignancies *[see Warnings and Precautions (5.2)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.3)]*
- Hepatitis B Virus Reactivation *[see Warnings and Precautions (5.4)]*
- Neurologic Reactions *[see Warnings and Precautions (5.5)]*
- Hematological Reactions *[see Warnings and Precautions (5.6)]*
- Heart Failure *[see Warnings and Precautions (5.8)]*
- Autoimmunity *[see Warnings and Precautions (5.9)]*

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 adalimumab was injection site reactions. In placebo-controlled trials, 20% of patients treated with adalimumab 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 adalimumab and 4% for placebo-treated patients. The most common adverse reactions leading to discontinuation of adalimumab in these RA studies were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%).

<u>Infections</u>

In the controlled portions of the 39 global adalimumab clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the rate of serious infections was 4.3 per 100 patient years in 7973 adalimumab treated patients versus a rate of 2.9 per 100 patient years in 4848 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 52 global controlled and uncontrolled clinical trials in RA, PsA, AS, CD, UC, Ps, HS and UV that included 24,605 adalimumab treated patients, the rate of reported active tuberculosis was 0.20 per 100 patient-years and the rate of positive PPD conversion was 0.09 per 100 patient-years. In a subgroup of 10,113 U.S. and Canadian adalimumab treated patients, the rate of reported active TB was 0.05 per 100 patient-years and the rate of positive PPD conversion was 0.07 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 0.05 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 adalimumab 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 adalimumab 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 adalimumab products 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 adalimumab (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 ≥ 3 x ULN occurred in 3.5% of adalimumab-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 adalimumab and the liver enzyme elevations is not clear. In a controlled Phase 3 trial of adalimumab in patients with polyarticular JIA who were 4 to 17 years, ALT elevations ≥ 3 x ULN occurred in 4.4% of adalimumab-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 adalimumab and MTX than those treated with adalimumab alone. In general, these elevations did not lead to discontinuation of adalimumab treatment. No ALT elevations ≥ 3 x ULN occurred in the open-label study of adalimumab in patients with polyarticular JIA who were 2 to < 4 years.

In controlled Phase 3 trials of adalimumab (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 Crohn’s Disease with a control period duration ranging from 4 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 0.9% of adalimumab-treated patients and 0.9% of control-treated patients. In the Phase 3 trial of adalimumab 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 ≥ 3 x 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

adalimumab (initial doses of 160 mg and 80 mg on Days 1 and 15 respectively, followed by 40 mg every other week) in adult patients with UC with control period duration ranging from 1 to 52 weeks, ALT elevations ≥3 x ULN occurred in 1.5% of adalimumab-treated patients and 1.0% of control-treated patients. In controlled Phase 3 trials of adalimumab (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 adalimumab-treated patients and 1.8% of control-treated patients. In controlled trials of adalimumab (initial doses of 80 mg at Week 0 followed by 40 mg every other week starting at Week 1) in adult patients with uveitis with an exposure of 165.4 PYs and 119.8 PYs in adalimumab-treated and control-treated patients, respectively, ALT elevations ≥ 3 x ULN occurred in 2.4% of adalimumab-treated patients and 2.4% of control-treated patients. In controlled trials of adalimumab (initial doses of 160 mg at Week 0 and 80 mg at Week 2, followed by 40 mg every week starting at Week 4), in subjects with HS with a control period duration ranging from 12 to 16 weeks, ALT elevations ≥ 3 x ULN occurred in 0.3% of adalimumab-treated subjects and 0.6% of control-treated subjects.

Other Adverse Reactions

Rheumatoid Arthritis Clinical Studies

The data described below reflect exposure to adalimumab 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). Adalimumab 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 adalimumab every other week *[see Clinical Studies (14.1)]*.

Table 1 summarizes reactions reported at a rate of at least 5% in patients treated with adalimumab 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 ≥5% of Patients Treated with Adalimumab During Placebo-Controlled Period of Pooled RA Studies (Studies RA-I, RA-II, RA-III, and RA-IV)

	Adalimumab 40 mg subcutaneous Every Other Week	**Placebo**
	(N=705)	(N=690)
Adverse Reaction (Preferred Term)		
Respiratory		
Upper respiratory infection	17%	13%
Sinusitis	11%	9%
Flu syndrome	7%	6%
Gastrointestinal		
Nausea	9%	8%

Abdominal pain	7%	4%
Laboratory Tests*		
Laboratory test abnormal	8%	7%
Hypercholesterolemia	6%	4%
Hyperlipidemia	7%	5%
Hematuria	5%	4%
Alkaline phosphatase increased	5%	3%
Other		
Headache	12%	8%
Rash	12%	6%
Accidental injury	10%	8%
Injection site reaction†	8%	1%
Back pain	6%	4%
Urinary tract infection	8%	5%
Hypertension	5%	3%

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

Less Common Adverse Reactions in Rheumatoid Arthritis Clinical Studies

Other infrequent serious adverse reactions that do not appear in the Warnings and Precautions or Adverse Reaction sections that occurred at an incidence of less than 5% in adalimumab-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 adalimumab-treated patients in the polyarticular juvenile idiopathic arthritis (JIA) trials (Studies JIA-I and JIA-II) *[see Clinical Studies (14.2)]* 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, adalimumab 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 adalimumab 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 adalimumab with or without concomitant MTX in the first 16 weeks of treatment. The types of infections reported in adalimumab-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 adalimumab were injection site pain and injection site reaction (19% and 16%, respectively). A less commonly reported adverse event in patients receiving adalimumab was granuloma annulare which did not lead to discontinuation of adalimumab 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 adalimumab 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 adalimumab 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 concentrations decreased or returned to normal in all patients. Most patients were able to continue adalimumab without interruption.

In Study JIA-II, adalimumab 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 adalimumab. 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 adalimumab 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

Adalimumab 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 *[see Clinical Studies (14.3, 14.4)]*. The safety profile for patients with PsA and AS treated with adalimumab 40 mg every other week was similar to the safety profile seen in patients with RA, adalimumab Studies RA-I through IV.

Crohn's Disease Clinical Studies

Adults

The safety profile of adalimumab in 1478 adult patients with Crohn's disease from four placebo-controlled and two open-label extension studies *[see Clinical Studies (14.5)]* was similar to the safety profile seen in patients with RA.

Pediatric Patients 6 Years to 17 Years

The safety profile of adalimumab in 192 pediatric patients from one double-blind study (Study PCD-I) and one open-label extension study *[see Clinical Studies (14.6)]* 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 adalimumab were injection site pain and injection site reaction (6% and 5%, respectively).

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

A total of 5% of children experienced a serious infection while receiving adalimumab 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

Adults: The safety profile of adalimumab in 1010 adult patients with ulcerative colitis (UC) from two placebo-controlled studies and one open-label extension study *[see Clinical Studies (14.7)]* was similar to the safety profile seen in patients with RA.

Plaque Psoriasis Clinical Studies

Adalimumab has been studied in 1696 subjects with plaque psoriasis (Ps) in placebo-controlled and open-label extension studies *[see Clinical Studies (14.9)]*. The safety profile for subjects with Ps treated with adalimumab was similar to the safety profile seen in subjects with RA with the following exceptions. In the placebo-controlled portions of the clinical trials in Ps subjects, adalimumab-treated subjects had a higher incidence of arthralgia when compared to controls (3% *vs.* 1%).

Hidradenitis Suppurativa Clinical Studies

Adalimumab has been studied in 727 subjects with hidradenitis suppurativa (HS) in three placebo-controlled studies and one open-label extension study *[see Clinical Studies (14.10)]*. The safety profile for subjects with HS treated with adalimumab weekly was consistent with the known safety profile of adalimumab.

Flare of HS, defined as ≥25% increase from baseline in abscesses and inflammatory nodule counts and with a minimum of 2 additional lesions, was documented in 22 (22%) of the 100 subjects who were withdrawn from adalimumab treatment following the primary efficacy timepoint in two studies.

Uveitis Clinical Studies

Adalimumab has been studied in 464 adult patients with uveitis (UV) in placebo-controlled and open-label extension studies *[see Clinical Studies (14.11)]*. The safety profile for patients with UV treated with adalimumab was similar to the safety profile seen in patients with RA.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other adalimumab products may be misleading.

There are two assays that have been used to measure anti-adalimumab antibodies. With the ELISA, antibodies to adalimumab could be detected only when serum adalimumab concentrations were < 2 mcg/mL. The ECL assay can detect anti-adalimumab antibody titers independent of adalimumab concentrations in the serum samples. The incidence of anti-adalimumab antibody (AAA) development in patients treated with adalimumab are presented in Table 2.

Table 2: Anti-Adalimumab Antibody Development Determined by ELISA and ECL Assay in Patients Treated with Adalimumab

Indications	**Study Duration**	**Anti-Adalimumab Antibody Incidence by ELISA (n/N)**		**Anti-Adalimumab Antibody Incidence by ECL Assay (n/N)**
		In all patients who received adalimumab	In patients with serum adalimumab concentrations < 2 mcg/mL	
Rheumatoid Arthritis*	6 to 12	5% (58/1062)	NR	NA

		months			
Juvenile Idiopathic Arthritis (JIA)	4 to 17 years of age†	48 weeks	16% (27/171)	NR	NA
	2 to 4 years of age or ≥ 4 years of age and weighing < 15 kg	24 weeks	7% (1/15)‡	NR	NA
Psoriatic Arthritis§		48 weeks¶	13% (24/178)	NR	NA
Ankylosing Spondylitis		24 weeks	9% (16/185)	NR	NA
Adult Crohn's Disease		56 weeks	3% (7/269)	8% (7/86)	NA
Pediatric Crohn's Disease		52 weeks	3% (6/182)	10% (6/58)	NA
Adult Ulcerative Colitis		52 weeks	5% (19/360)	21% (19/92)	NA
Plaque Psoriasis#		Up to 52 weeksÞ	8% (77/920)	21% (77/372)	NA
Hidradenitis Suppurativa		36 weeks	7% (30/461)	28% (58/207)ß	61% (272/445)à
Non-infectious Uveitis		52 weeks	5% (12/249)	21% (12/57)	40% (99/240)è

n: number of patients with anti-adalimumab antibody; NR: not reported; NA: Not applicable (not performed)

* In patients receiving concomitant methotrexate (MTX), the incidence of anti-adalimumab antibody was 1% compared to 12% with adalimumab monotherapy
† In patients receiving concomitant MTX, the incidence of anti-adalimumab antibody was 6% compared to 26% with adalimumab monotherapy
‡ This patient received concomitant MTX
§ In patients receiving concomitant MTX, the incidence of antibody development was 7% compared to 1% in RA
¶ Subjects enrolled after completing 2 previous studies of 24 weeks or 12 weeks of treatments.
# In plaque psoriasis patients who were on adalimumab monotherapy and subsequently withdrawn from the treatment, the rate of antibodies to adalimumab after retreatment was similar to the rate observed prior to withdrawal
Þ One 12-week Phase 2 study and one 52-week Phase 3 study
ß Among subjects in the 2 Phase 3 studies who stopped adalimumab treatment for up to 24 weeks and in whom adalimumab serum levels subsequently declined to <2 mcg/mL (approximately 22% of total subjects studied)
à No apparent association between antibody development and safety was observed
è No correlation of antibody development to safety or efficacy outcomes was observed

Rheumatoid Arthritis and Psoriatic Arthritis

Patients in Studies RA-I, RA-II, and RA-III were tested at multiple time points for antibodies to adalimumab using the ELISA during the 6- to 12- month period. 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 adalimumab products is unknown.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of adalimumab products. 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 adalimumab products 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, lichenoid skin reaction

Vascular disorders: Systemic vasculitis, deep vein thrombosis

7 DRUG INTERACTIONS

7.1 Methotrexate

Adalimumab 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 HULIO 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 observed with the combination of TNF blockers with anakinra or abatacept, with no added benefit; therefore, use of HULIO with abatacept or anakinra is not recommended in patients with RA *[see Warnings and Precautions (5.7, 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 HULIO and other biologic products for the treatment of RA, PsA, AS, CD, UC, Ps, HS and UV. Concomitant administration of HULIO 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 HULIO *[see Warnings and Precautions (5.10)].*

7.4 Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased concentrations of cytokines (e.g., TNFα, IL-6) during chronic inflammation. It is possible for products that antagonize cytokine activity, such as adalimumab products, to influence the formation of CYP450 enzymes. Upon initiation or discontinuation of HULIO 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

Risk Summary

Available studies with use of adalimumab during pregnancy do not reliably establish an association between adalimumab and major birth defects. Clinical data are available from the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry in pregnant women with rheumatoid arthritis (RA) or Crohn’s disease (CD) treated with adalimumab. Registry results showed a rate of 10% for major birth defects with first trimester use of adalimumab in pregnant women with RA or CD and a rate of 7.5% for major birth defects in the disease matched comparison cohort. The lack of pattern of major birth defects is reassuring and differences between exposure groups may have impacted the occurrence of birth defects *(see Data).*

Adalimumab is actively transferred across the placenta during the third trimester of pregnancy and may affect immune response in the *in-utero* exposed infant *(see Clinical Considerations).* In an embryo-fetal perinatal development study conducted in cynomolgus monkeys, no fetal harm or malformations were observed with intravenous administration of adalimumab during organogenesis and later in gestation, at doses that produced exposures up to approximately 373 times the maximum recommended human dose (MRHD) of 40 mg subcutaneous without methotrexate *(see Data).*

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and embryo/fetal risk

Published data suggest that the risk of adverse pregnancy outcomes in women with RA or inflammatory bowel disease (IBD) is associated with increased disease activity. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Fetal/Neonatal Adverse Reactions

Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester *(see Data)*. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to adalimumab products *in utero [see Use in Specific Populations (8.4)]*.

Data

Human Data

A prospective cohort pregnancy exposure registry conducted by OTIS/MotherToBaby in the U.S. and Canada between 2004 and 2016 compared the risk of major birth defects in live-born infants of 221 women (69 RA, 152 CD) treated with adalimumab during the first trimester and 106 women (74 RA, 32 CD) not treated with adalimumab.

The proportion of major birth defects among live-born infants in the adalimumab-treated and untreated cohorts was 10% (8.7% RA, 10.5% CD) and 7.5% (6.8% RA, 9.4% CD), respectively. The lack of pattern of major birth defects is reassuring and differences between exposure groups may have impacted the occurrence of birth defects. This study cannot reliably establish whether there is an association between adalimumab and major birth defects because of methodological limitations of the registry, including small sample size, the voluntary nature of the study, and the non-randomized design.

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

Animal Data

In an embryo-fetal perinatal development study, pregnant cynomolgus monkeys received adalimumab from gestation days 20 to 97 at doses that produced exposures up to 373 times that achieved with the MRHD without methotrexate (on an AUC basis with maternal IV doses up to 100 mg/kg/week). Adalimumab did not elicit harm to the fetuses or malformations.

8.2 Lactation

Risk Summary

Limited data from case reports in the published literature describe the presence of adalimumab in human milk at infant doses of 0.1% to 1% of the maternal serum

concentration. Published data suggest that the systemic exposure to a breastfed infant is expected to be low because adalimumab is a large molecule and is degraded in the gastrointestinal tract. However, the effects of local exposure in the gastrointestinal tract are unknown. There are no reports of adverse effects of adalimumab products on the breastfed infant and no effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HULIO and any potential adverse effects on the breastfed child from HULIO or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of HULIO have been established for:

- reducing signs and symptoms of moderately to severely active polyarticular JIA in pediatric patients 2 years of age and older.
- the treatment of moderately to severely active Crohn's disease in pediatric patients 6 years of age and older.

Pediatric assessments for HULIO demonstrate that HULIO is safe and effective for pediatric patients in indications for which Humira (adalimumab) is approved. However, HULIO is not approved for such indications due to marketing exclusivity for Humira (adalimumab).

Due to their inhibition of TNFα, adalimumab products administered during pregnancy could affect immune response in the in utero-exposed newborn and infant. Data from eight infants exposed to adalimumab in utero suggest adalimumab crosses the placenta *[see Use in Specific Populations (8.1)]*. The clinical significance of elevated adalimumab concentrations 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 adalimumab products *[see Warnings and Precautions (5.2)]*.

<u>Juvenile Idiopathic Arthritis</u>

In Study JIA-I, adalimumab 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)]*. Adalimumab products have 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 adalimumab in patients in the polyarticular JIA trials was generally similar to that observed in adults with certain exceptions *[see Adverse Reactions (6.1)]*.

The safety and effectiveness of adalimumab products have not been established in pediatric patients with JIA less than 2 years of age.

<u>Pediatric Crohn's Disease</u>

The safety and effectiveness of adalimumab products for the treatment of moderately

to severely active Crohn's disease have been established in pediatric patients 6 years of age and older. Use of adalimumab products for this indication is supported by evidence from adequate and well-controlled studies in adults with additional data from a randomized, double-blind, 52-week clinical study of two dose concentrations of adalimumab in 192 pediatric patients (6 years to 17 years of age) *[see Adverse Reactions (6.1), Clinical Pharmacology (12.2, 12.3), Clinical Studies (14.6)]*. The adverse reaction profile in patients 6 years to 17 years of age was similar to adults.

The safety and effectiveness of adalimumab products have 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 adalimumab 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 adalimumab treated patients 65 years of age and older was higher than for those less than 65 years of age. Consider the benefits and risks of HULIO in patients 65 years of age and older. In patients treated with HULIO, closely monitor for the development of infection or malignancy *[see Warnings and Precautions (5.1, 5.2)]*.

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

Adalimumab-fkjp is a tumor necrosis factor blocker. Adalimumab-fkjp is a recombinant human IgG1 monoclonal antibody. Adalimumab-fkjp is produced by recombinant DNA technology in a mammalian cell expression system (Chinese Hamster Ovary Cells) 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.

HULIO (adalimumab-fkjp) injection is supplied as a sterile, preservative-free solution for subcutaneous administration. The drug product is supplied as either a single-dose, prefilled pen (HULIO Pen) or as a single-dose, 1 mL prefilled plastic syringe. Enclosed within the pen is a single- dose, 1 mL prefilled plastic syringe. The solution of HULIO is clear to slightly opalescent, colorless to pale brownish-yellow, with a pH of about 5.2.

Each 40 mg/0.8 mL prefilled syringe or prefilled pen delivers 0.8 mL (40 mg) of drug product. Each 0.8 mL of HULIO contains adalimumab-fkjp (40 mg), methionine (0.60 mg), monosodium glutamate (1.50 mg), polysorbate 80 (0.80 mg), sorbitol (38.2 mg) and Water for Injection, USP. Hydrochloric acid 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 HULIO contains adalimumab-fkjp (20 mg), methionine (0.30 mg), monosodium glutamate (0.75 mg), polysorbate 80 (0.40 mg), sorbitol (19.1 mg) and Water for

Injection, USP. Hydrochloric acid is added as necessary to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Adalimumab products bind specifically to TNF-alpha and block its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab products also lyse surface TNF expressing cells *in vitro* in the presence of complement. Adalimumab products do not bind or inactivate lymphotoxin (TNF-beta). TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated concentrations 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 concentrations of TNF are also found in psoriasis plaques. In Ps, treatment with HULIO may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamic activities and the mechanism(s) by which adalimumab products exert their clinical effects is unknown.

Adalimumab products also modulate biological responses that are induced or regulated by TNF, including changes in the concentrations of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC50 of 1-2 X 10^{-10}M).

12.2 Pharmacodynamics

After treatment with adalimumab, a decrease in concentrations 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 concentrations was also observed in patients with Crohn’s disease, ulcerative colitis and hidradenitis suppurativa. Serum concentrations of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodeling responsible for cartilage destruction were also decreased after adalimumab administration.

12.3 Pharmacokinetics

The pharmacokinetics of adalimumab were linear over the dose range of 0.5 to 10 mg/kg following administration of a single intravenous dose (adalimumab products are not approved for intravenous use). Following 20, 40, and 80 mg every other week and every week subcutaneous administration, adalimumab mean serum trough concentrations at steady state increased approximately proportionally with dose in RA patients. The mean terminal half-life was approximately 2 weeks, ranging from 10 to 20 days across studies. Healthy subjects and patients with RA displayed similar adalimumab pharmacokinetics.

Adalimumab exposure in patients treated with 80 mg every other week is estimated to be comparable with that in patients treated with 40 mg every week.

<u>Absorption</u>

The average absolute bioavailability of adalimumab following a single 40 mg subcutaneous dose was 64%. The mean time to reach the maximum concentration was 5.5 days (131 ± 56 hours) and the maximum serum concentration was 4.7 ± 1.6 mcg/mL in healthy subjects following a single 40 mg subcutaneous administration of

adalimumab.

Distribution

The distribution volume (Vss) ranged from 4.7 to 6.0 L following intravenous administration of doses ranging from 0.25 to 10 mg/kg in RA patients.

Elimination

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 systemic clearance of adalimumab is approximately 12 mL/hr. In long-term studies with dosing more than two years, there was no evidence of changes in clearance over time in RA patients.

Patient Population

Rheumatoid Arthritis and Ankylosing Spondylitis

In patients receiving 40 mg adalimumab every other week, adalimumab mean steady-state trough concentrations were approximately 5 mcg/mL and 8 to 9 mcg/mL, without and with MTX concomitant treatment, respectively. Adalimumab concentrations in the synovial fluid from five rheumatoid arthritis patients ranged from 31 to 96% of those in serum. The pharmacokinetics of adalimumab in patients with AS were similar to those in patients with RA.

Psoriatic Arthritis

In patients receiving 40 mg every other week, adalimumab mean steady-state trough concentrations were 6 to 10 mcg/mL and 8.5 to 12 mcg/mL, without and with MTX concomitant treatment, respectively.

Plaque Psoriasis

Adalimumab mean steady-state trough concentration was approximately 5 to 6 mcg/mL during adalimumab 40 mg every other week treatment.

Adult Hidradenitis Suppurativa

Adalimumab trough concentrations were approximately 7 to 8 mcg/mL at Week 2 and Week 4, respectively, after receiving 160 mg on Week 0 followed by 80 mg on Week 2. Mean steady-state trough concentrations at Week 12 through Week 36 were approximately 7 to 11 mcg/mL during adalimumab 40 mg every week treatment.

Adult Uveitis

Adalimumab mean steady concentration was approximately 8 to 10 mcg/mL during adalimumab 40 mg every other week treatment.

Adult Crohn’s Disease

Adalimumab mean trough concentrations were approximately 12 mcg/mL at Week 2 and Week 4 after receiving 160 mg on Week 0 followed by 80 mg on Week 2. Mean steady-state trough concentrations were 7 mcg/mL at Week 24 and Week 56 during

adalimumab 40 mg every other week treatment.

Adult Ulcerative Colitis

Adalimumab mean trough concentrations were approximately 12 mcg/mL at Week 2 and Week 4 after receiving 160 mg on Week 0 followed by 80 mg on Week 2. Mean steady-state trough concentrations were approximately 8 mcg/mL and 15 mcg/mL at Week 52 after receiving a dose of adalimumab 40 mg every other week and 40 mg every week, respectively.

Anti-Drug Antibody Effects on Pharmacokinetics

Rheumatoid Arthritis

A trend toward higher apparent clearance of adalimumab in the presence of anti-adalimumab antibodies was identified.

Hidradenitis Suppurativa

In subjects with moderate to severe HS, antibodies to adalimumab were associated with reduced serum adalimumab concentrations. In general, the extent of reduction in serum adalimumab concentrations is greater with increasing titers of antibodies to adalimumab.

Specific Populations

Geriatric Patients

A lower clearance with increasing age was observed in patients with RA aged 40 to >75 years.

Pediatric Patients

Juvenile Idiopathic Arthritis:

- *4 years to 17 years of age:* The adalimumab mean steady-state trough concentrations were 6.8 mcg/mL and 10.9 mcg/mL in patients weighing <30 kg receiving 20 mg adalimumab subcutaneously every other week as monotherapy or with concomitant MTX, respectively. The adalimumab mean steady-state trough concentrations were 6.6 mcg/mL and 8.1 mcg/mL in patients weighing ≥30 kg receiving 40 mg adalimumab subcutaneously every other week as monotherapy or with MTX concomitant treatment, respectively.
- *2 years to <4 years of age or 4 years of age and older weighing <15 kg:* The adalimumab mean steady-state trough adalimumab concentrations were 6.0 mcg/mL and 7.9 mcg/mL in patients receiving adalimumab subcutaneously every other week as monotherapy or with MTX concomitant treatment, respectively.

*Pediatric Crohn's Disease:*Adalimumab mean ± SD concentrations were 15.7±6.5 mcg/mL at Week 4 following 160 mg at Week 0 and 80 mg at Week 2, and 10.5±6.0 mcg/mL at Week 52 following 40 mg every other week dosing in patients weighing ≥ 40 kg. Adalimumab mean ± SD concentrations were 10.6±6.1 mcg/mL at Week 4 following dosing 80 mg at Week 0 and 40 mg at Week 2, and 6.9±3.6 mcg/mL at Week 52 following 20 mg every other week dosing in patients weighing < 40 kg.

Male and Female Patients

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

Patients with Renal or Hepatic Impairment

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

Rheumatoid factor or CRP concentrations

Minor increases in apparent clearance were 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.

Drug Interaction Studies

Methotrexate: MTX reduced adalimumab apparent clearance after single and multiple dosing by 29% and 44% respectively, in patients with RA *[see Drug Interactions (7.1)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies of adalimumab products have not been conducted to evaluate the carcinogenic potential or its effect on fertility.

14 CLINICAL STUDIES

14.1 Rheumatoid Arthritis

The efficacy and safety of adalimumab were assessed in five randomized, double-blind studies in patients ≥18 years of age with active rheumatoid arthritis (RA) diagnosed according to American College of Rheumatology (ACR) criteria. Patients had at least 6 swollen and 9 tender joints. Adalimumab 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 adalimumab 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 adalimumab 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 adalimumab every other week with placebo injections on alternate weeks, or 20 mg of adalimumab 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 adalimumab was administered every other week for up to 5 years.

Study RA-IV assessed safety in 636 patients who were either DMARD-naive or were permitted to remain on their pre-existing rheumatologic therapy provided that therapy was stable for a minimum of 28 days. Patients were randomized to 40 mg of adalimumab 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), adalimumab 40 mg every other week or adalimumab/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 adalimumab treated patients achieving ACR 20, 50 and 70 responses in Studies RA-II and III are shown in Table 3.

Table 3. ACR Responses in Studies RA-II and RA-III (Percent of Patients)

	Study RA-II Monotherapy (26 weeks)			**Study RA-III Methotrexate Combination (24 and 52 weeks)**	
Response	Placebo	Adalimumab	Adalimumab	Placebo/MTX	Adalimumab/MTX
		40 mg every	40 mg weekly		40 mg every
		other week			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%*

* $p<0.01$, adalimumab *vs.* placebo

The results of Study RA-I were similar to Study RA-III; patients receiving adalimumab 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 4. 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

adalimumab patients receiving 40 mg every other week achieved a major clinical response, defined as maintenance of an ACR 70 response over a 6-month period. ACR responses were maintained in similar proportions of patients for up to 5 years with continuous adalimumab treatment in the open-label portion of Study RA-III.

Table 4. Components of ACR Response in Studies RA-II and RA-III

	Study RA-II				**Study RA-III**			
Parameter (median)	**Placebo N=110**		**Adalimumab* N=113**		**Placebo/MTX N=200**		**Adalimumab*/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‡	7.0	6.1	6.6	3.7†	6.3	3.5	6.5	2.0†
Patient global assessment‡	7.5	6.3	7.5	4.5†	5.4	3.9	5.2	2.0†
Pain‡	7.3	6.1	7.3	4.1†	6.0	3.8	5.8	2.1†
Disability index (HAQ)§	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†

* 40 mg adalimumab administered every other week
† $p<0.001$, adalimumab *vs.* placebo, based on mean change from baseline
‡ Visual analogue scale; 0 = best, 10 = worst
§ 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

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.

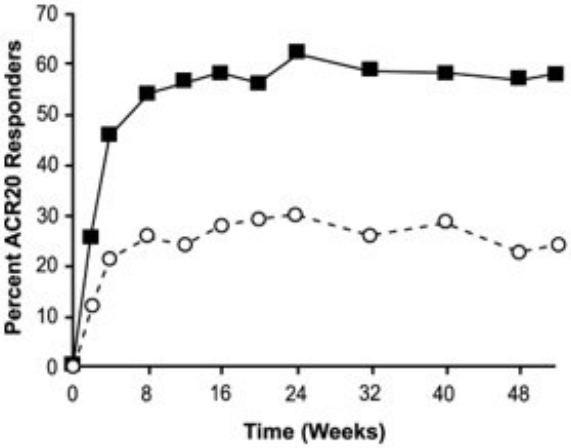


Figure 1. Study RA-III ACR 20 Responses over 52 Weeks

In Study RA-IV, 53% of patients treated with adalimumab 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 adalimumab and other DMARDs were observed.

In Study RA-V with MTX naïve patients with recent onset RA, the combination treatment with adalimumab plus MTX led to greater percentages of patients achieving ACR responses than either MTX monotherapy or adalimumab monotherapy at Week 52 and responses were sustained at Week 104 (see Table 5).

Table 5. ACR Response in Study RA-V (Percent of Patients)

Response	**MTX*** **N=257**	**Adalimumab†** **N=274**	**Adalimumab/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‡	28%	25%	49%

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

At Week 52, all individual components of the ACR response criteria for Study RA-V improved in the adalimumab/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 6. Adalimumab/MTX treated patients demonstrated less radiographic progression than patients receiving MTX alone at 52 weeks.

Table 6. Radiographic Mean Changes Over 12 Months in Study RA-III

	Placebo/MTX	**Adalimumab/MTX 40 mg every other week**	**Placebo/MTX-Adalimumab/ 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 adalimumab.
† Based on rank analysis

In the open-label extension of Study RA-III, 77% of the original patients treated with any dose of adalimumab 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 adalimumab 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 adalimumab/MTX combination group as compared to either the MTX or adalimumab monotherapy group at Week 52 as well as at Week 104 (see Table 7).

Table 7. Radiographic Mean Change* in Study RA-V

		MTX† N=257	**Adalimumab†‡ N=274**	**Adalimumab/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)
† p<0.001, adalimumab/MTX *vs.* MTX at 52 and 104 weeks and for adalimumab/MTX *vs.* adalimumab at 104 weeks
‡ p<0.01, for adalimumab/MTX *vs.* adalimumab at 52 weeks

Physical Function Response

In studies RA-I through IV, adalimumab 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 adalimumab patients and 0.25 (0.17, 0.33) for placebo/MTX ($p<0.001$) patients. Sixty-three percent of adalimumab-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 adalimumab/MTX combination therapy group versus either the MTX monotherapy or the adalimumab monotherapy group at Week 52, which was maintained through Week 104.

14.2 Juvenile Idiopathic Arthritis

The safety and efficacy of adalimumab was assessed in two studies (JIA-I and JIA-II) in patients with active polyarticular juvenile idiopathic arthritis (JIA).

Study JIA-I

The safety and efficacy of adalimumab 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, adalimumab was administered based on body surface area at a dose of 24 mg/m^2 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 adalimumab SC every other week if their weight was less than 30 kg and with 40 mg of adalimumab 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 adalimumab or placebo every other week for 32 weeks or until disease flare. Disease flare was defined as a worsening of ≥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 adalimumab experienced disease flare compared to placebo, both without MTX (43% *vs.* 71%) and with MTX (37% *vs.* 65%). More patients treated with adalimumab 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 adalimumab throughout the study.

Study JIA-II

Adalimumab 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 adalimumab treatment dosed 24 mg/m^2 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 adalimumab 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 adalimumab 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 adalimumab 40 mg or placebo every other week were administered during the 24-week double-blind period of the study.

Compared to placebo, treatment with adalimumab resulted in improvements in the measures of disease activity (see Tables 8 and 9). Among patients with PsA who received adalimumab, 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 adalimumab 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 8. ACR Response in Study PsA-I (Percent of Patients)

	Placebo N=162	**Adalimumab* 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 adalimumab and placebo

Table 9. Components of Disease Activity in Study PsA-I

	Placebo N=162		**Adalimumab* N=151**	
Parameter: median	Baseline	24 weeks	Baseline	24 weeks
Number of tender joints†	23.0	17.0	20.0	5.0
Number of swollen joints‡	11.0	9.0	11.0	3.0
Physician global assessment§	53.0	49.0	55.0	16.0
Patient global assessment§	49.5	49.0	48.0	20.0
Pain§	49.0	49.0	54.0	20.0
Disability index (HAQ)¶	1.0	0.9	1.0	0.4
CRP (mg/dL)#	0.8	0.7	0.8	0.2

* $p<0.001$ for adalimumab *vs.* placebo comparisons based on median changes
† Scale 0-78
‡ Scale 0-76
§ Visual analog scale; 0=best, 100=worst
¶ 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.
# 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 adalimumab or placebo and at Week 48 when all patients were on open-label adalimumab. 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.

Adalimumab-treated patients demonstrated greater inhibition of radiographic progression compared to placebo-treated patients and this effect was maintained at 48 weeks (see Table 10).

Table 10. Change in Modified Total Sharp Score in Psoriatic Arthritis

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

* <0.001 for the difference between adalimumab, 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 adalimumab 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 adalimumab 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 adalimumab 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 adalimumab 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 11.

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

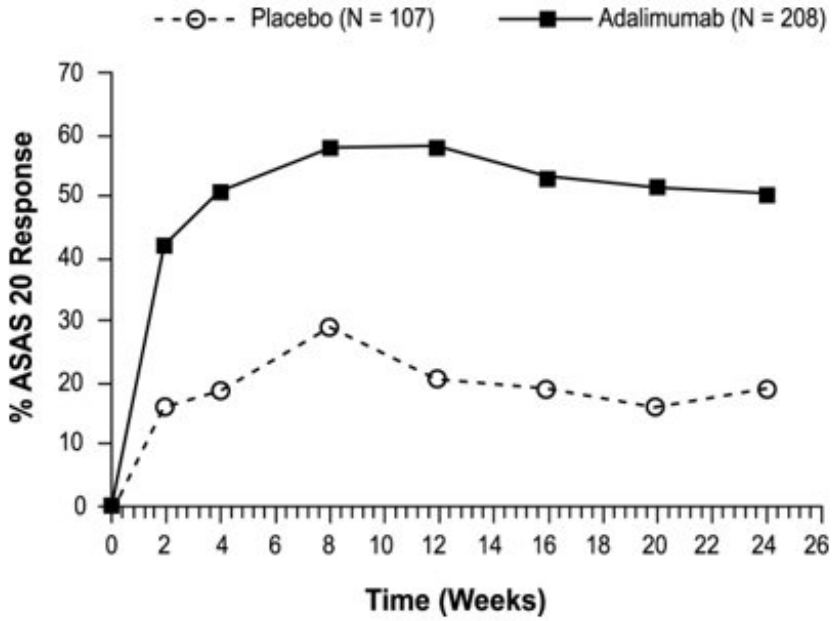


Figure 2. ASAS 20 Response By Visit, Study AS-I

At 12 weeks, the ASAS 20/50/70 responses were achieved by 58%, 38%, and 23%, respectively, of patients receiving adalimumab, 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 adalimumab for up to 52 weeks.

A greater proportion of patients treated with adalimumab (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 11. Components of Ankylosing Spondylitis Disease Activity

	Placebo N=107		**Adalimumab N=208**	
	Baseline mean	**Week 24 mean**	**Baseline mean**	**Week 24 mean**
ASAS 20 Response Criteria*				
Patient's Global Assessment of Disease Activity†*	65	60	63	38
Total back pain*	67	58	65	37
Inflammation‡*	6.7	5.6	6.7	3.6

BASFI§*	56	51	52	34
BASDAI¶ score*	6.3	5.5	6.3	3.7
BASMI# 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
CRPÞ*	2.2	2.0	1.8	0.6

* statistically significant for comparisons between adalimumab and placebo at Week 24
† 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”
‡ mean of questions 5 and 6 of BASDAI (defined in ‘d’)
§ Bath Ankylosing Spondylitis Functional Index
¶ Bath Ankylosing Spondylitis Disease Activity Index
# Bath Ankylosing Spondylitis Metrology Index
Þ C-Reactive Protein (mg/dL)

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

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

Induction of clinical remission (defined as CDAI < 150) was evaluated in two studies. In Study CD-I, 299 TNF-blocker naïve patients were randomized to one of four treatment groups: the placebo group received placebo at Weeks 0 and 2, the 160/80 group received 160 mg adalimumab 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 adalimumab 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 adalimumab, 80 mg at week 0 and 40 mg at Week 2. Patients were then randomized at Week 4 to 40 mg adalimumab every other week, 40 mg adalimumab 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 adalimumab 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 12).

Table 12. Induction of Clinical Remission in Studies CD-I and CD-II (Percent of Patients)

	CD-I		**CD-II**	
	Placebo N=74	**Adalimumab 160/80 mg N=76**	**Placebo N=166**	**Adalimumab 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 adalimumab *vs.* placebo pairwise comparison of proportions
† p<0.01 for adalimumab *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 adalimumab 40 mg every other week maintenance group compared to patients in the placebo maintenance group (see Table 13). The group that received adalimumab therapy every week did not demonstrate significantly higher remission rates compared to the group that received adalimumab every other week.

Table 13. Maintenance of Clinical Remission in CD-III (Percent of Patients)

	Placebo	**40 mg Adalimumab 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 adalimumab vs. placebo pairwise comparisons of proportions

Of those in response at Week 4 who attained remission during the study, patients in the adalimumab 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 concentrations of adalimumab (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). 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 ≤ 10).

The proportions of patients in clinical remission (defined as PCDAI ≤ 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 14). The recommended maintenance regimen is 20 mg every other week for patients weighing < 40 kg and 40 mg every other week for patients weighing ≥ 40 kg. Every week dosing is not the recommended maintenance dosing regimen *[see Dosage and Administration (2.3)]*.

Table 14. 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 ≥ 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 ≥ 40 kg and 20 mg every other week for patients weighing < 40 kg.
‡ Clinical remission defined as PCDAI ≤ 10.
§ Clinical response defined as reduction in PCDAI of at least 15 points from baseline.

14.7 Adult Ulcerative Colitis

The safety and efficacy of adalimumab 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 adalimumab at Week 0 and

80 mg at Week 2, and the 80/40 group received 80 mg adalimumab at Week 0 and 40 mg at Week 2. After Week 2, patients in both adalimumab treatment groups received 40 mg every other week.

In Study UC-II, 518 patients were randomized to receive either adalimumab 160 mg at Week 0, 80 mg at Week 2, and 40 mg every other week starting at Week 4 through Week 50, or placebo starting at Week 0 and every other week 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 adalimumab 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 adalimumab compared to patients treated with placebo achieved sustained clinical remission (clinical remission at both Weeks 8 and 52) (Table 15).

Table 15. 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	**Adalimumab 160/80 mg N=130**	**Treatment Difference (95% CI)**	**Placebo N=246**	**Adalimumab 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 adalimumab *vs.* placebo pairwise comparison of proportions

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

In Study UC-II, 17.3% (43/248) in the adalimumab 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 adalimumab group versus 7% (7/101) in the placebo group, and sustained clinical remission at 5% (5/98) in the adalimumab 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 adalimumab group versus 3% (3/101) in the placebo group.

14.9 Plaque Psoriasis

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

Study Ps-I evaluated 1212 subjects with chronic Ps with ≥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, subjects received placebo or adalimumab 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, subjects 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 adalimumab every other week. After 17 weeks of open label therapy, subjects 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 adalimumab 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 subjects randomized to adalimumab and 48 subjects randomized to placebo with chronic plaque psoriasis with ≥10% BSA involvement and PASI ≥12. Subjects received placebo, or an initial dose of 80 mg adalimumab 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 subjects who achieved "clear" or "minimal" disease on the 6-point PGA scale and the proportion of subjects who achieved a reduction in PASI score of at least 75% (PASI 75) from baseline at Week 16 (see Table 17 and 18).

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

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

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

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

Table 18. Efficacy Results at 16 Weeks in Study Ps-II Number of Subjects (%)

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

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

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

Additionally, in Study Ps-I, subjects on adalimumab who maintained a PASI 75 were re-randomized to adalimumab (N = 250) or placebo (N = 240) at Week 33. After 52 weeks of treatment with adalimumab, more subjects on adalimumab 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 adalimumab, then 40 mg every other week beginning at week 1. At week 16, 69% (123/178) of subjects had a response of PGA “clear” or “minimal”.

A randomized, double-blind study (Study Ps-III) compared the efficacy and safety of adalimumab versus placebo in 217 adult subjects. Subjects in the study had to have chronic plaque psoriasis of at least moderate severity on the PGA scale, fingernail involvement of at least moderate severity on a 5-point Physician’s Global Assessment of Fingernail Psoriasis (PGA-F) scale, a Modified Nail Psoriasis Severity Index (mNAPSI) score for the target-fingernail of ≥ 8, and either a BSA involvement of at least 10% or a BSA involvement of at least 5% with a total mNAPSI score for all fingernails of ≥ 20. Subjects received an initial dose of 80 mg adalimumab followed by 40 mg every other week (starting one week after the initial dose) or placebo for 26 weeks followed by open-label adalimumab treatment for an additional 26 weeks. This study evaluated the proportion of subjects who achieved “clear” or “minimal” assessment with at least a 2-grade improvement on the PGA-F scale and the proportion of subjects who achieved at least a 75% improvement from baseline in the mNAPSI score (mNAPSI 75) at Week 26.

At Week 26, a higher proportion of subjects in the adalimumab group than in the placebo group achieved the PGA-F endpoint. Furthermore, a higher proportion of subjects in the adalimumab group than in the placebo group achieved mNAPSI 75 at

Week 26 (see Table 19).

Table 19. Efficacy Results at 26 Weeks

Endpoint	**Adalimumab 40 mg every other week*** **N=109**	**Placebo** **N=108**
PGA-F: ≥2-grade improvement and *clear* or *minimal*	49%	7%
mNAPSI 75	47%	3%

* Subjects received 80 mg of adalimumab at Week 0, followed by 40 mg every other week starting at Week 1.

Nail pain was also evaluated and improvement in nail pain was observed in Study Ps-III.

14.10 Hidradenitis Suppurativa

Two randomized, double-blind, placebo-controlled studies (Studies HS-I and II) evaluated the safety and efficacy of adalimumab in a total of 633 adult subjects with moderate to severe hidradenitis suppurativa (HS) with Hurley Stage II or III disease and with at least 3 abscesses or inflammatory nodules. In both studies, subjects received placebo or adalimumab at an initial dose of 160 mg at Week 0, 80 mg at Week 2, and 40 mg every week starting at Week 4 and continued through Week 11. Subjects used topical antiseptic wash daily. Concomitant oral antibiotic use was allowed in Study HS-II.

Both studies evaluated Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12. HiSCR was defined as at least a 50% reduction in total abscess and inflammatory nodule count with no increase in abscess count and no increase in draining fistula count relative to baseline (see Table 18). Reduction in HS-related skin pain was assessed using a Numeric Rating Scale in patients who entered the study with an initial baseline score of 3 or greater on a 11 point scale.

In both studies, a higher proportion of adalimumab- than placebo-treated subjects achieved HiSCR (see Table 20).

Table 20. Efficacy Results at 12 Weeks in Subjects with Moderate to Severe Hidradenitis Suppurativa

	HS Study 1		**HS Study 2***	
	Placebo	**Adalimumab 40 mg Weekly**	**Placebo**	**Adalimumab 40 mg Weekly**
Hidradenitis Suppurativa Clinical Response (HiSCR)	N = 154 40 (26%)	N = 153 64 (42%)	N=163 45 (28%)	N=163 96 (59%)

* 19.3% of subjects in Study HS-II continued baseline oral antibiotic therapy during the study.

In both studies, from Week 12 to Week 35 (Period B), subjects who had received

adalimumab were re-randomized to 1 of 3 treatment groups (adalimumab 40 mg every week, adalimumab 40 mg every other week, or placebo). Subjects who had been randomized to placebo were assigned to receive adalimumab 40 mg every week (Study HS-I) or placebo (Study HS-II).

During Period B, flare of HS, defined as ≥25% increase from baseline in abscesses and inflammatory nodule counts and with a minimum of 2 additional lesions, was documented in 22 (22%) of the 100 subjects who were withdrawn from adalimumab treatment following the primary efficacy timepoint in two studies.

14.11 Adult Uveitis

The safety and efficacy of adalimumab were assessed in adult patients with non-infectious intermediate, posterior and panuveitis excluding patients with isolated anterior uveitis, in two randomized, double-masked, placebo-controlled studies (UV I and II). Patients received placebo or adalimumab at an initial dose of 80 mg followed by 40 mg every other week starting one week after the initial dose. The primary efficacy endpoint in both studies was ´time to treatment failure´.

Treatment failure was a multi-component outcome defined as the development of new inflammatory chorioretinal and/or inflammatory retinal vascular lesions, an increase in anterior chamber (AC) cell grade or vitreous haze (VH) grade or a decrease in best corrected visual acuity (BCVA).

Study UV I evaluated 217 patients with active uveitis while being treated with corticosteroids (oral prednisone at a dose of 10 to 60 mg/day). All patients received a standardized dose of prednisone 60 mg/day at study entry followed by a mandatory taper schedule, with complete corticosteroid discontinuation by Week 15.

Study UV II evaluated 226 patients with inactive uveitis while being treated with corticosteroids (oral prednisone 10 to 35 mg/day) at baseline to control their disease. Patients subsequently underwent a mandatory taper schedule, with complete corticosteroid discontinuation by Week 19.

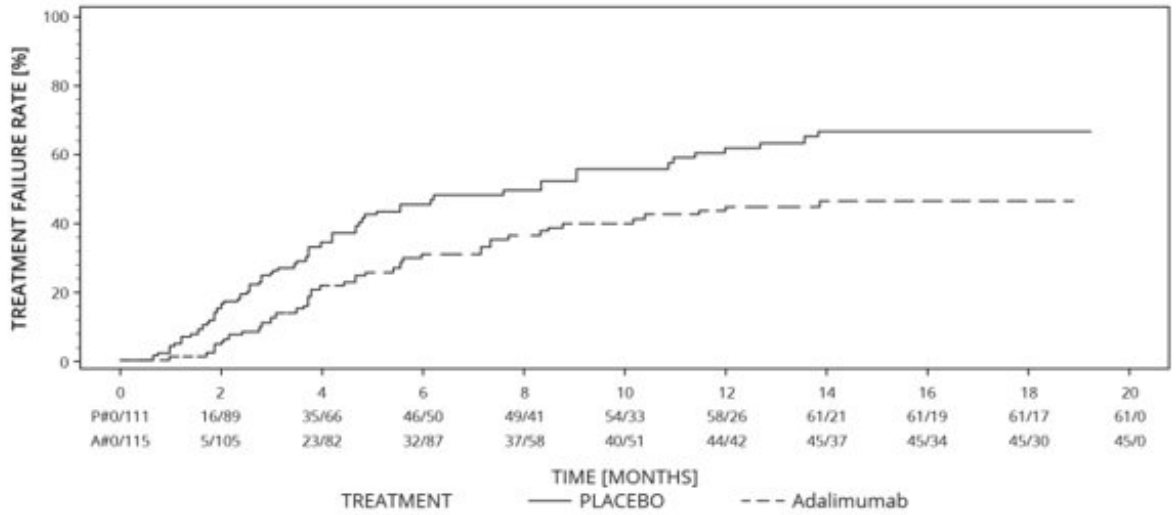
Clinical Response

Results from both studies demonstrated statistically significant reduction of the risk of treatment failure in patients treated with adalimumab versus patients receiving placebo. In both studies, all components of the primary endpoint contributed cumulatively to the overall difference between adalimumab and placebo groups (Table 21).

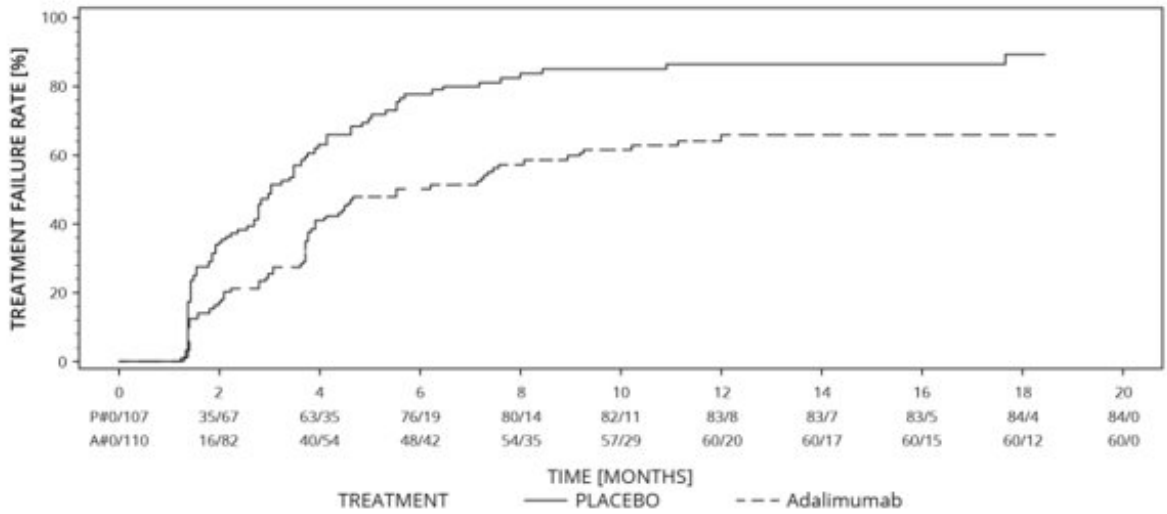
Table 21. Time to Treatment Failure in Studies UV I and UV II

	UV I			**UV II**		
	Placebo (N = 107)	Adalimumab (N = 110)	HR [95% CI]*	Placebo (N = 111)	Adalimumab (N = 115)	HR [95% CI]*
Failure† n (%)	84 (78.5)	60 (54.5)	0.50 [0.36, 0.70]	61 (55.0)	45 (39.1)	0.57 [0.39, 0.84]
Median Time to Failure (Months) [95% CI]	3.0 [2.7, 3.7]	5.6 [3.9, 9.2]	N/A	8.3 [4.8, 12.0]	NE‡	N/A

* HR of adalimumab versus placebo from proportional hazards regression with treatment as factor.
† Treatment failure at or after Week 6 in Study UV I, or at or after Week 2 in Study UV II, was counted as event. Subjects who discontinued the study were censored at the time of dropping out.
‡ NE = not estimable. Fewer than half of at-risk subjects had an event.



Study UV I



Study UV II

Figure 3: Kaplan-Meier Curves Summarizing Time to Treatment Failure on or after Week 6 (Study UV I) or Week 2 (Study UV II)

Note: P# = Placebo (Number of Events/Number at Risk); A# = Adalimumab (Number of Events/Number at Risk).

15 REFERENCES

1. National Cancer Institute. Surveillance, Epidemiology, and End Results Database (SEER) Program. SEER Incidence Crude Rates, 17 Registries, 2000-2007.

16 HOW SUPPLIED/STORAGE AND HANDLING

HULIO® (adalimumab-fkjp) injection is supplied as a preservative-free, sterile, clear to slightly opalescent and colorless to pale brownish-yellow solution for subcutaneous administration. The following packaging configurations are available:

HULIO Prefilled Syringe Carton - 20 mg/0.4 mL

> HULIO is supplied in a carton containing two alcohol preps and two dose trays. Each dose tray consists of a single-dose, 1 mL pre-filled plastic syringe with a fixed 29 gauge thin wall, ½ inch needle, providing 20 mg/0.4 mL of HULIO. The NDC number is 49502-381-02.

HULIO Prefilled Syringe Carton - 40 mg/0.8 mL

> HULIO is supplied in a carton containing two alcohol preps and two dose trays. Each dose tray consists of a single-dose, 1 mL prefilled plastic syringe with a fixed 29 gauge thin wall, ½ inch needle, providing 40 mg/0.8 mL of HULIO. The NDC number is 49502-382-02.

HULIO Prefilled Pen Carton - 40 mg/0.8 mL

> HULIO is supplied in a carton containing two alcohol preps and two dose trays. Each dose tray consists of a single-dose pen, containing a 1 mL prefilled plastic syringe with a fixed 29 gauge thin wall, ½ inch needle, providing 40 mg/0.8 mL of HULIO. The NDC number is 49502-380-02.

Storage and Stability

Do not use beyond the expiration date on the container. HULIO 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, HULIO 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. HULIO should be discarded if not used within the 14-day period. Record the date when HULIO is first removed from the refrigerator in the spaces provided on the carton and dose tray.

Do not store HULIO in extreme heat or cold.

17 PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Infections

Inform patients that HULIO may lower the ability of their immune system to fight infections. Instruct patients of the importance of contacting their healthcare provider if they develop any symptoms of infection, including tuberculosis, invasive fungal

infections, and reactivation of hepatitis B virus infections *[see Warnings and Precautions (5.1, 5.2, 5.4)]*.

Malignancies

Counsel patients about the risk of malignancies while receiving HULIO *[see Warnings and Precautions (5.2)]*.

Hypersensitivity Reactions

Advise patients to seek immediate medical attention if they experience any symptoms of severe hypersensitivity reactions.

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 *[see Warnings and Precautions (5.5, 5.6, 5.8, 5.9)]*.

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 HULIO, instruct them in injection techniques and assess their ability to inject subcutaneously to ensure the proper administration of HULIO *[see Instructions for Use].*

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

- Will hear two "clicks" during the Hulio injection. The first ‘click’ means the **start** of injection and second ‘click’ means the **end** of injection.
- To start injection, push the Pen body down. Continue holding down after hearing the first ‘click’.
- In the viewing window, the orange indicator will advance to show the progress of the injection.
- When injection has finished, there will be a second ‘click’ and the ‘Orange Indicator’ will completely block the viewing window.

Instruct patients to dispose of their used needles and syringes or used Pen in an 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 an 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.

MEDICATION GUIDE

HULIO®(hue lee oh) **(adalimumab-fkjp)** **injection, for subcutaneous use**
Read the Medication Guide that comes with HULIO 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 healthcare provider about your medical condition or treatment.

What is the most important information I should know about HULIO?
HULIO is a medicine that affects your immune system. HULIO can lower the ability of your immune system to fight infections. **Serious infections have happened in people taking adalimumab products. 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 healthcare provider should test you for TB before starting HULIO.
- Your healthcare provider should check you closely for signs and symptoms of TB during treatment with HULIO.

You should not start taking HULIO if you have any kind of infection unless your healthcare provider says it is okay.
Before starting HULIO, tell your healthcare provider if you:

- think you have an infection or have symptoms of an infection such as:
  - fever, sweats, or chills
  - muscle aches
  - cough
  - shortness of breath
  - blood in phlegm
  - 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
  - weight loss
- 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 healthcare provider 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 HULIO. Ask your healthcare

provider 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 HULIO, call your healthcare provider right away if you have an infection, or any sign of an infection.
HULIO can make you more likely to get infections or make any infection that you may have worse.
Cancer

- For children and adults taking Tumor Necrosis Factor (TNF)-blockers, including HULIO, 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 rheumatoid arthritis (RA), especially more serious RA, may have a higher chance for getting a kind of cancer called lymphoma.
- If you use TNF blockers including HULIO 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 healthcare provider if you have a bump or open sore that does not heal.
- Some people receiving TNF blockers including HULIO 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).

What is HULIO?
HULIO is a medicine called a Tumor Necrosis Factor (TNF) blocker. HULIO is used:

- To reduce the signs and symptoms of:
    - **moderate to severe RA in adults.** HULIO 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. HULIO can be used alone or with methotrexate.
    - **psoriatic arthritis (PsA) in adults.** HULIO can be used alone or with certain other medicines.
    - **ankylosing spondylitis (AS) in adults.**
    - **moderate to severe hidradenitis suppurativa (HS) in adults.**

- **To treat moderate to severe Crohn’s disease (CD) in adults and children 6 years of age and older.**
- **To treat moderate to severe ulcerative colitis (UC) in adults.** It is not known if adalimumab products are 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).
- **To treat non-infectious intermediate, posterior, and panuveitis in adult patients.**

What should I tell my healthcare provider before taking HULIO?
HULIO may not be right for you. Before starting HULIO, tell your healthcare provider about all of your medical conditions, including if you:

- have an infection. See **"What is the most important information I should know about HULIO?"**
- 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 HULIO. Children should be brought up to date with all vaccines before starting HULIO.
- are allergic to HULIO or to any of its ingredients. See the end of this Medication Guide for a list of ingredients in HULIO.
- are pregnant or plan to become pregnant, breastfeeding or plan to breastfeed. You and your healthcare provider should decide if you should take HULIO while you are pregnant or breastfeeding.
- have a baby and you were using HULIO during your pregnancy. Tell your baby's healthcare provider before your baby receives any vaccines.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Especially tell your healthcare provider if you use:

- ORENCIA (abatacept), KINERET (anakinra), REMICADE (infliximab), ENBREL (etanercept), CIMZIA (certolizumab pegol) or SIMPONI (golimumab), because you should not use HULIO while you are also using one of these medicines.
- RITUXAN (rituximab). Your healthcare provider may not want to give you HULIO 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 healthcare provider and pharmacist each time you get a new medicine.

How should I take HULIO?

- HULIO is given by an injection under the skin. Your healthcare provider will tell you how often to take an injection of HULIO. This is based on your condition to be treated. **Do not inject HULIO 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 HULIO.
- Make sure you have been shown how to inject HULIO before you do it yourself. You can call your healthcare provider or 1-800-796-9526 if you have any questions about giving yourself an injection. Someone you know can also help you with your injection after they have been shown how to prepare and inject HULIO.
- **Do not** try to inject HULIO yourself until you have been shown the right way to give the injections. If your healthcare provider decides that you or a caregiver may

be able to give your injections of HULIO at home, you should receive training on the right way to prepare and inject HULIO.

- **Do not** miss any doses of HULIO unless your healthcare provider says it is okay. If you forget to take HULIO, 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 HULIO, call your healthcare provider or pharmacist.
- If you take more HULIO than you were told to take, call your healthcare provider.

What are the possible side effects of HULIO?
HULIO can cause serious side effects, including:
See "What is the most important information I should know about HULIO?"

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

  - 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 HULIO. Your healthcare provider should do blood tests before you start treatment, while you are using HULIO, and for several months after you stop treatment with HULIO. Tell your healthcare provider 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 HULIO. Call your healthcare provider or get medical help right away if you have any of these symptoms of a serious allergic reaction:

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

- **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 healthcare provider right away** if you get new worsening symptoms of heart failure while taking HULIO, including:

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

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

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

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

Call your healthcare provider or get medical care right away if you develop any of the above symptoms. Your treatment with HULIO may be stopped.
The most common side effects of HULIO include:

- injection site reactions: redness, rash, swelling, itching, or bruising. These symptoms usually will go away within a few days. Call your healthcare provider 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.

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

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

How should I store HULIO?

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

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

General information about the safe and effective use of HULIO.
Medicines are sometimes prescribed for purposes other than those listed in a Medication
Guide. Do not use HULIO for a condition for which it was not prescribed. Do not give HULIO to other people, even if they have the same condition. It may harm them.
This Medication Guide summarizes the most important information about HULIO. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about HULIO that is written for health professionals.

What are the ingredients in HULIO?
Active ingredient: adalimumab-fkjp
HULIO Pen 40 mg/0.8 mL, HULIO 40 mg/0.8 mL prefilled syringe, HULIO 20 mg/0.4 mL prefilled syringe.
Inactive ingredients: methionine, monosodium glutamate, polysorbate 80, sorbitol and Water for Injection. Hydrochloric acid is added as necessary to adjust pH.
Manufactured by: **Mylan Pharmaceuticals Inc.**, Morgantown, WV 26505 U.S.A.
Manufactured for: **Mylan Specialty L.P.**, Morgantown, WV 26505 U.S.A.
Product of Japan
U.S. License Number 2210
For more information, call Mylan at 1-877-446-3679 (1-877-4-INFO-RX) or you can enroll in a patient support program by calling 1-800-796-9526.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 08/2023

Manufactured by:
Mylan Pharmaceuticals Inc.

Morgantown, WV 26505 U.S.A.

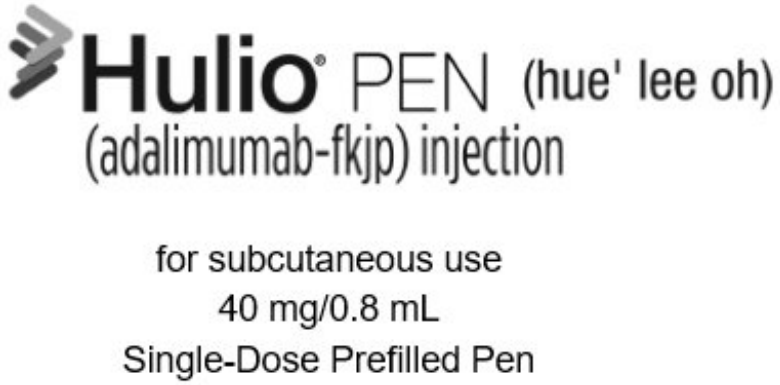
Manufactured for:
Mylan Specialty L.P.
Morgantown, WV 26505 U.S.A.

U.S. License No. 2210

Product of Japan

PCI:ADAL:RX14

INSTRUCTIONS FOR USE



For subcutaneous (under the skin) use only

Read these instructions carefully before using your Pen. This information does not replace talking to your healthcare provider about your medical condition and your treatment.

Do not try to inject HULIO yourself until you have been shown the right way to give the injections and have read and understand this Instructions for Use. If your healthcare provider decides that you or a caregiver may be able to give your injections of HULIO at home, you should receive training on the right way to prepare and inject HULIO. It is important that you read, understand, and follow these instructions so that you inject HULIO the right way. It is also important to talk to your healthcare provider to be sure you understand your HULIO dosing instructions. To help you remember when to inject HULIO, 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 HULIO.

For Questions or Assistance, Call Mylan at 1-877-446-3679 (1-877-4-INFO-RX)

Caution:
Never put your thumb, fingers, or hand over the orange activator after cap is removed. Never press or push the Orange Activator with your thumb, fingers, or hand. The Orange Activator is where the needle comes out. If accidental injection to your fingers or hands occurs, apply first-aid and either call your healthcare provider or go to the nearest hospital emergency room if needed.

Dosage:
HULIO PEN is for single dose (1-time) use only.

Important:

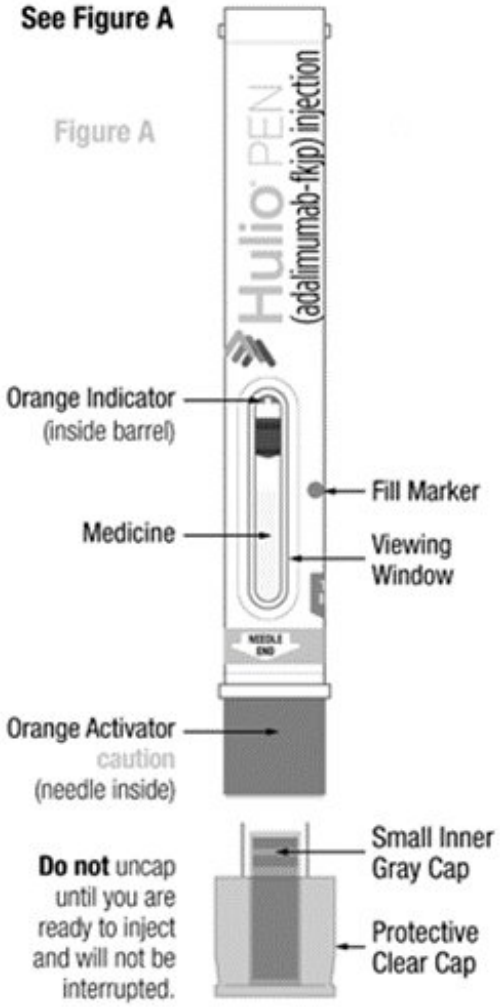
Do not use HULIO if frozen, even if it has been thawed.

Do not uncap your HULIO PEN until you are ready to inject and will not be interrupted.
Do not recap. Recapping your HULIO PEN can damage the needle.

A loud “click” will occur when the Orange Activator is pressed down to deliver your dose of HULIO.

- You must practice injecting with your healthcare provider or nurse so that you are not surprised by this “click” sound when you give yourself injections.
- This 1st “click” sound means the start of the injection.
- You will know that the injection has finished when all three of these have occurred:
    - A 2nd “click” was heard, and
    - Orange Indicator has stopped and completely blocked the Viewing Window, and
    - 10 seconds has passed.

Parts of the HULIO PEN



Storing and Handling the HULIO PEN

- **Store Pen in a refrigerator between 36°F to 46°F (2°C to 8°C) in its original carton.**
- Refrigerated HULIO may be used until the expiration date.
- **Do not** freeze the Pen.
- **Do not** expose the Pen to extreme heat or cold, such as a hot car, or a freezing car overnight.

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

- **Protect from light.**
- **Take care not to drop or crush.**
- **Do not** use if the Pen is damaged or broken.
- **Keep HULIO, injection supplies, and all other medicines out of the reach of children.**

Gather Supplies for Injection

Find a quiet area with a well-lit, clean and flat work surface and gather all the supplies you will need to give yourself or receive an injection.

Supplies you will need:

Included in HULIO carton

- 1 Pen (taken from refrigerator 30 minutes prior to intended injection time to allow Pen to reach room temperature.)
- 1 alcohol prep

Not included in HULIO carton

- 1 FDA-cleared sharps disposal container or puncture resistant container. (See **"How should I throw away (dispose of) the used HULIO PEN and Cap?"** Section in Step 7 at the end of this Instructions for Use).
- 1 gauze pad or cotton ball

If you do not have all the supplies you need to give yourself an injection, visit or call your local pharmacist.

Preparing the Pen

Remove the Pen from the refrigerator 30 minutes before using.

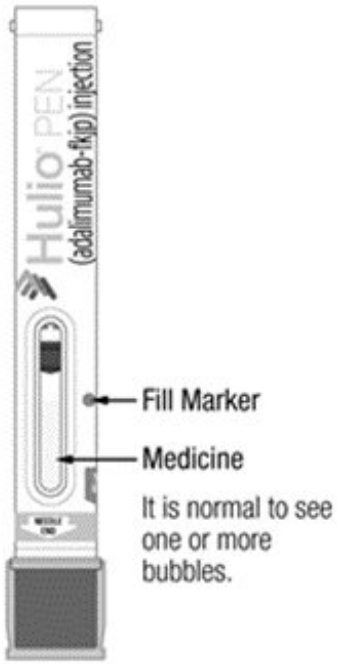
- Make sure the name HULIO appears on the Pen label.
- **Check the expiration date printed on the Pen (See Figure B).**
- **Do not** use the Pen past the expiration date.
- **Check that the HULIO PEN has not been frozen or left in direct sunlight.**
- **Let the Pen reach room temperature.**
- **Do not** use external heat sources such as hot water, direct sunlight, or microwave to warm the Pen.
- **Do not** put the Pen back in the refrigerator after it has reached room temperature.

Figure B

Check the Viewing Window to make sure:

- **Medicine is at or near the Fill Marker. You may need to shake gently to see liquid.**
- **Medicine is clear and colorless to pale brownish-yellow (See Figure C).**

Figure C



Do not use the Pen if medicine is not near the Fill Marker. Use another Pen or contact your healthcare provider.
Do not use the Pen if it is cloudy, discolored, or has particles in it.

Choosing and Preparing Injection Site

Your healthcare provider should show you proper injection site techniques.

- **Recommended subcutaneous (under the skin) injection sites are:**
  - **the front of the thighs, or**
  - **the abdomen (belly)**
  - **Do not** use area within 2 inches of belly button (See Figure D).

Figure D

- **You should rotate and change your injection site each time you give an injection.**
- Stay at least 1 inch from a previous site used.
- **Do not** inject into areas where the skin is tender, bruised, red, hard, scarred or has stretch marks.
- If you have psoriasis, **do not** inject into any raised, thick, red, or scaly skin patches or lesions.
- **Do not** inject through clothes. Roll back any clothing that may get in the way of the injection site.

- **Wash your hands with soap and water.**
- **Wipe the chosen injection site using a circular motion with an alcohol prep.** Wait for it to dry on its own, do not blow dry.
- **Do not** touch this injection site again before receiving your injection.

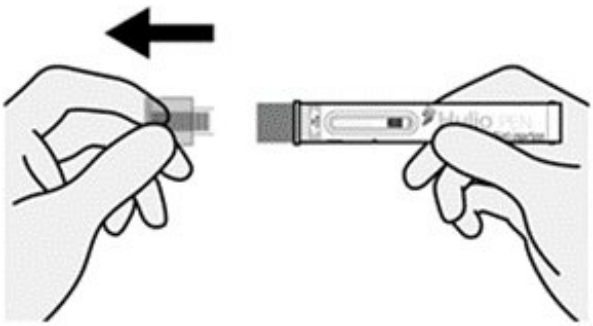
Giving the Injection

Caution: Injection process must be completed without interruption.
Read all steps first before beginning injection.

Step 1

Uncap

Figure E



- **Pull straight on the protective clear cap to uncap the Pen (See Figure E). Do not twist.**
- A few drops of liquid may come out of the needle, this is normal.
- Throw away the protective clear cap in an FDA-cleared sharps container or puncture resistant container (See "**How should I throw away (dispose of) the used HULIO PEN and Cap?**" in Step 7). **Do not** put your protective clear cap in the household trash.

Important:

- **Do not** put the protective clear cap back on the Pen. This can damage the needle.
- **Do not** touch the Orange Activator with your fingers (this is where the needle comes out).

Step 2

Squeeze and Hold Injection Site

The thigh injection site is shown here (See Figure F). Perform these steps the same way for abdomen (belly) injection sites.

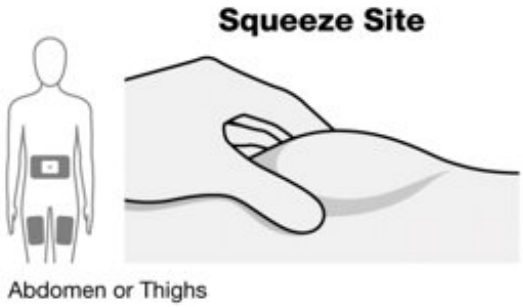


Figure F

- **Squeeze the injection site to create a raised area, and hold that area firmly until the injection is complete.**
- **See "Choosing and Preparing Injection Site"** or talk to your healthcare provider for injection site assistance.

Step 3

Place Pen

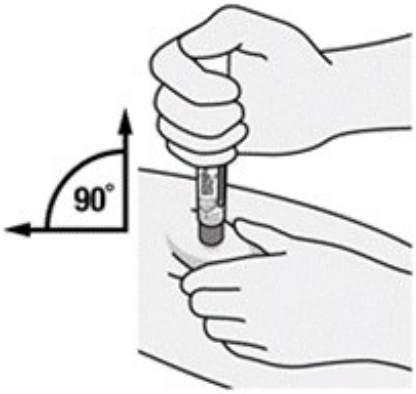


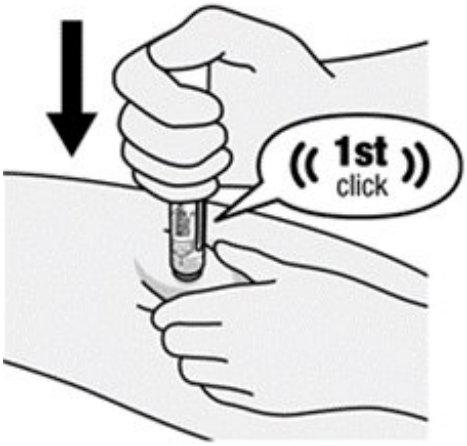
Figure G

- **Place the Orange Activator end onto the injection site.**
- **Keep the Pen held straight (90° angle) and flat to the raised injection site area, and with the Viewing Window visible to you (See Figure G).**
- Be careful to place the Pen so that it will not inject into your fingers holding the injection site.

Step 4

Begin Injection

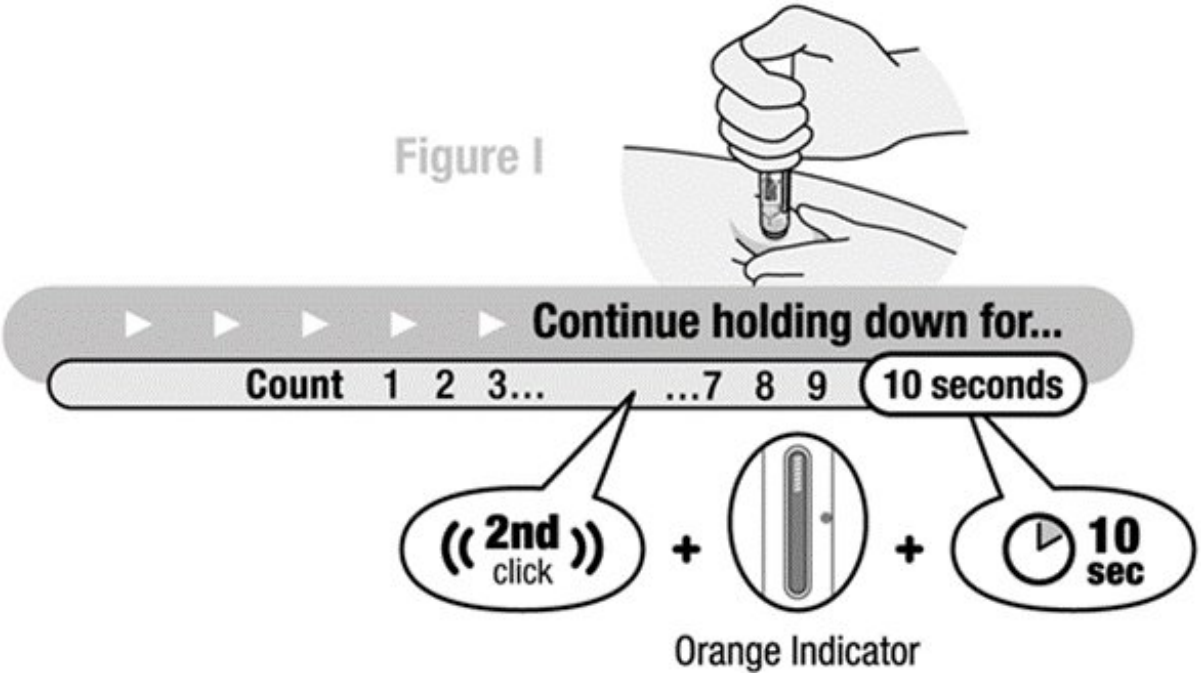
Figure H



- **Firmly push the body of the Pen down against the injection site to engage the Orange Activator and begin injection (See Figure H).** Try not to cover the Viewing Window.
- **Continue pushing down after hearing the 1st "click".** This 1st "click" sound signals the start of the injection.
- **In the Viewing Window, the Orange-Indicator will move to show the progress of the injection.**
- **Do not** move, twist, or rotate the Pen during injection.

Step 5

Hold Down for 2nd "click", Orange Indicator and 10 Seconds



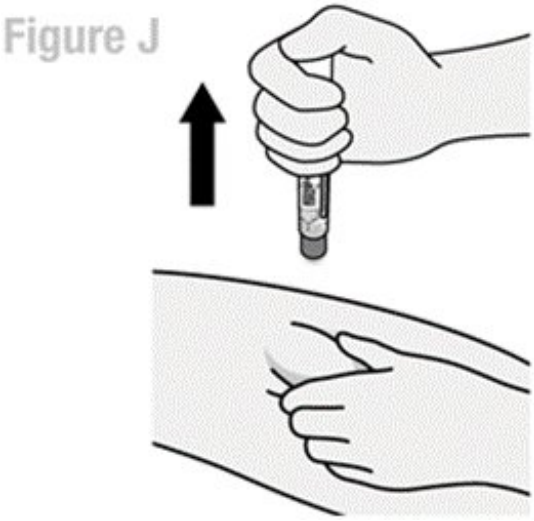
Continue pushing the body of the Pen down against the injection site until:

- A 2nd “click” was heard, and
- Orange Indicator has stopped and completely blocked the Viewing Window (See Figure I), and
- 10 seconds has passed.

Caution: Make sure all three of these have occurred to ensure all medicine was delivered. If the needle did not retract or you do not think you received the full dose, contact your healthcare provider for assistance.

Step 6

End of Injection, Remove HULIO PEN



- **Pull Pen straight away from the injection site (See Figure J).**
- There may be a small amount of liquid on the injection site. This is normal. If slight bleeding occurs from the injection site, press a gauze pad or cotton ball lightly against the site for a few seconds.
- **Do not** rub the injection site.

Dispose of the HULIO PEN and Cap
Put the used Pen and Cap in an FDA-cleared sharps disposal container or puncture resistant container right away to avoid injury (See “How should I throw away (dispose of) the used HULIO PEN and Cap?” in Step 7).
Pen is for single-dose only.
Do not reuse the Pen if all of the medicine was not injected.
Do not try to recap the Pen as it could lead to a needle stick injury.

Step 7

How should I throw away (dispose of) the used HULIO PEN and Cap?

- **Put your used Pen and Cap in an FDA-cleared sharps disposal container right away after use.**
- **Do not throw away (dispose of) the Pen or Cap in your household trash.**

If you do not have an 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 pens. 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.
Do not recycle your used sharps disposal container.

Step 8

Write down the date you received your injection and the injection site used in the injection diary.

Injection Diary

Date	Injection Site Used

Customer Service
For Questions or Assistance,
Call Mylan at 1-877-446-3679 (1-877-4-INFO-RX)

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The Hulio Logo is a trademark of BGP Products Operations GmbH, a Viatris Company.

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Manufactured by:

Mylan Pharmaceuticals Inc.

Morgantown, WV 26505 U.S.A.

Manufactured for:

Mylan Specialty L.P.

Morgantown, WV 26505 U.S.A.

U.S. License No. 2210

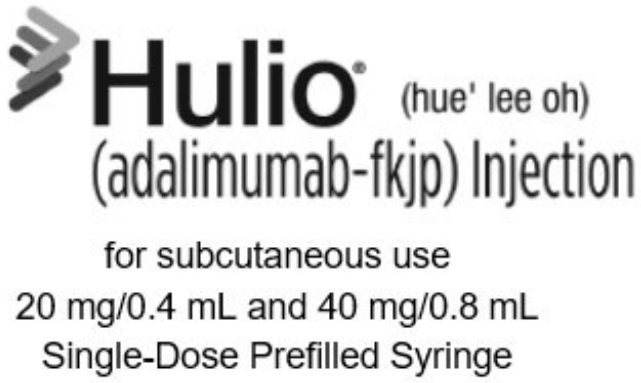
Product of Japan

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

Revised: 11/2022
PCI:ADAL:IFUP:RX6

697892

INSTRUCTIONS FOR USE



For subcutaneous (under the skin) use only

Read these instructions carefully before using your Syringe. This information does not replace talking to your healthcare provider about your medical condition and your treatment.

Do not try to inject HULIO yourself until you have been shown the right way to give the injections and have read and understand this Instructions for Use. If your healthcare

provider decides that you or a caregiver may be able to give your injections of HULIO at home, you should receive training on the right way to prepare and inject HULIO. It is important that you read, understand, and follow these instructions so that you inject HULIO the right way. It is also important to talk to your healthcare provider to be sure you understand your HULIO dosing instructions. To help you remember when to inject HULIO, 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 HULIO.

For Questions or Assistance, Call Mylan at 1-877-446-3679 (1-877-4-INFO-RX)

Dosage:
HULIO Prefilled Syringe is for single dose (1-time) use only.

Important:

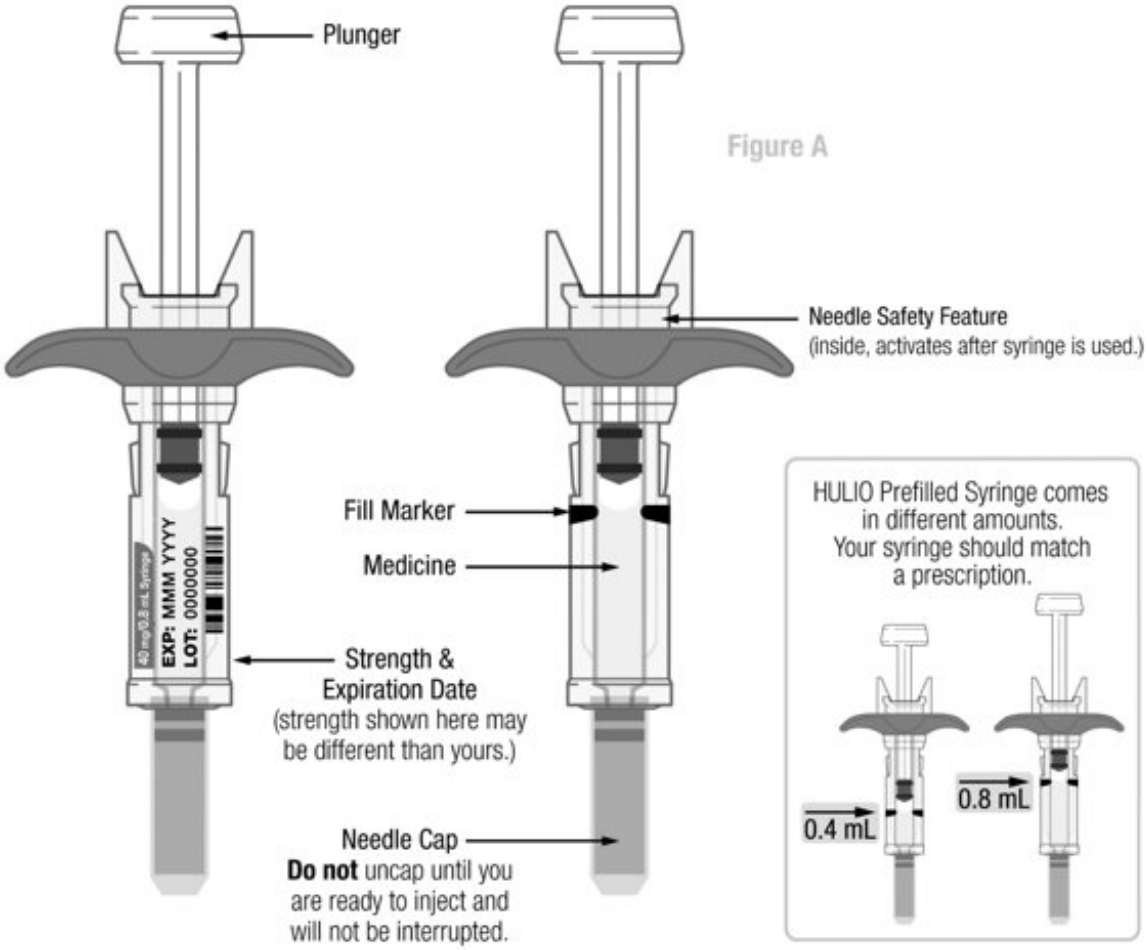
- **Do not** use HULIO if frozen, even if it has been thawed.

- **Do not** uncap your HULIO Prefilled Syringe until you are ready to inject and will not be interrupted.

- **Do not** recap. Recapping your HULIO Prefilled Syringe can damage the needle.

Parts of the HULIO Prefilled Syringe (Syringe)

See Figure A



Storing and Handling the Syringe

- **Store Syringe in a refrigerator between 36°F to 46°F (2°C to 8°C) in its original carton.**
- Refrigerated HULIO may be used until the expiration date.
- **Do not** freeze the Syringe.
- **Do not** expose the Syringe to extreme heat or cold, such as a hot car, or a freezing car overnight.

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

- **Protect from light.**
- **Take care not to drop or crush.**
- **Do not** use if the Syringe is damaged or broken.
- **Keep HULIO, injection supplies, and all other medicines out of the reach of children.**

Gather Supplies for Injection

Find a quiet area with a well-lit, clean and flat work surface and gather all the supplies you will need to give yourself or receive an injection.

Supplies you will need:

Included in the HULIO carton

- 1 Syringe
  (taken from refrigerator 30 minutes prior to intended injection time to allow Syringe to reach room temperature)
- 1 alcohol prep

Not included in HULIO carton

- 1 FDA-cleared sharps disposal container or puncture resistant container (See "**How should I throw away (dispose of) the used HULIO Prefilled Syringe and Needle Cap?**" Section in Step 6 at the end of this Instructions for Use.)
- 1 gauze pad or cotton ball

If you do not have all the supplies you need to give yourself an injection, visit or call your local pharmacist.

Preparing the Syringe

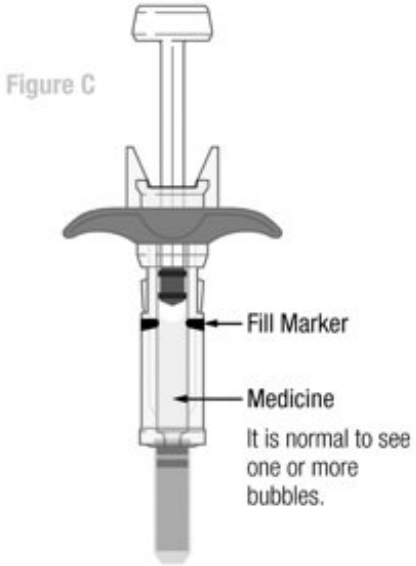
Remove the Syringe from the refrigerator 30 minutes before using.

- Make sure the name HULIO appears on the Syringe label.
- **Check the expiration date printed on the Syringe (See Figure B).**
- **Do not** use the Syringe past the expiration date.
- **Check that the Syringe has not been frozen or left in direct sunlight.**
- **Let the Syringe reach room temperature.**
- **Do not** use external heat sources such as hot water, direct sunlight, or microwave to warm the Syringe.
- **Do not** put the Syringe back in the refrigerator after it has reached room temperature.

Figure B

Check the Viewing Window to make sure:

- **Medicine is at or near the Fill Marker.** You may need to shake gently to see liquid.
- **Medicine is clear and colorless to pale brownish-yellow (See Figure C).**



Do not use the Syringe if medicine is not near the Fill Marker. Use another Syringe or contact your healthcare provider.

Do not use the Syringe if it is cloudy, discolored, or has particles in it.

Choosing and Preparing Injection Site

Your healthcare provider should show you proper injection site techniques.

- **Recommended subcutaneous (under the skin)**
- **injection sites are:**
    - **the front of the thighs, or**
    - **the abdomen (belly)**
    - **Do not** use area within 2 inches of belly button (See Figure D).

- **You should rotate and change your injection**
- **site each time you give an injection.**
- Stay at least 1 inch from a previous site used.
- **Do not** inject into areas where the skin is tender,
- bruised, red, hard, scarred or has stretch marks.
- If you have psoriasis, **do not** inject into any raised,
- thick, red, or scaly skin patches or lesions.
- **Do not** inject through clothes. Roll back any clothing that may get in the way of the injection site.

Figure D

- **Wash your hands with soap and water.**
- **Wipe the chosen injection site using a circular**
- **motion with an alcohol prep.** Wait for it to dry on its own, do not fan or blow dry.
- **Do not** touch this injection site again before receiving your injection.

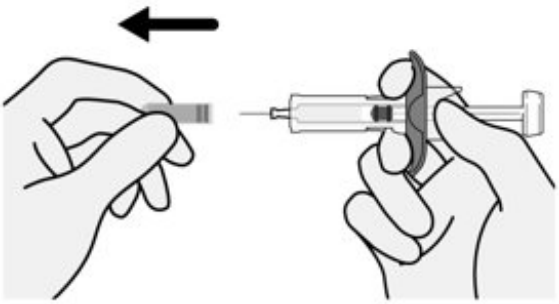
Giving the Injection

Caution: Injection process must be completed without interruption.
Read all steps first before beginning injection.

Step 1

Uncap

Figure E



- **Pull straight on the Needle Cap to uncap the Syringe (See Figure E). Do not twist.**
- A few drops of liquid may come out of the needle, this is normal.
- It is normal to see one or more air bubble(s).
- Throw away the Needle Cap in an FDA-cleared sharps container or puncture resistant container (See **"How should I throw away (dispose of) the used HULIO Prefilled Syringe and Needle Cap?"** in Step 6). **Do not** put your protective clear cap in the household trash.

Caution:

- **Do not** recap Syringe.
- **Do not** remove air bubble(s).
- **Do not** pull back on the Plunger at any time.
- **Do not** touch the needle with your fingers or let the needle touch anything.
- **Do not** use Syringe if dropped after uncapping.

Step 2

Squeeze and Hold Injection Site

The thigh injection site is shown here (See Figure F). Perform these steps the same way for abdomen (belly) injection sites.

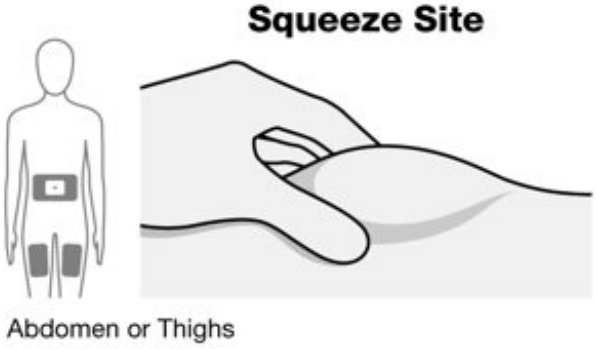


Figure F

- **Squeeze the injection site to create a raised area, and hold that area firmly until the injection is complete.**
- **See "Choosing and Preparing Injection Site"** or talk to your healthcare provider for injection site assistance.

Step 3

Insert Needle Into Site

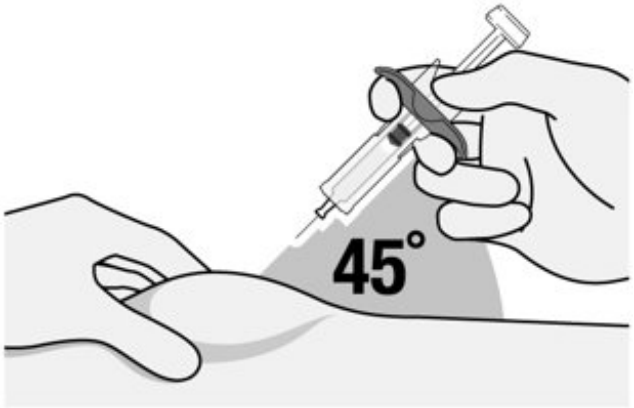


Figure G

At a 45° angle to the injection site, with your other hand use a quick dart-like motion to insert the needle into the site (See Figure G).
Be careful to insert the needle so that it will not inject into your fingers holding the injection site.

Step 4

Inject Medicine

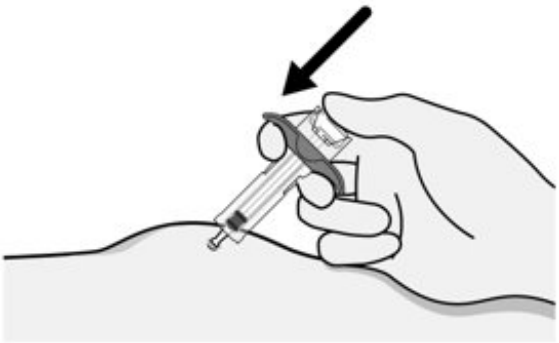


Figure H

After the needle is in, let go of squeezing the injection site.
Slowly push the plunger all the way down with your thumb until all the medicine is injected and the Syringe is empty (See Figure H). If the plunger is not pressed all the way down the Needle Safety Feature will not activate afterwards to cover the needle.
Do not move, twist, or rotate Syringe during injection.

Step 5

End of Injection, Remove Syringe

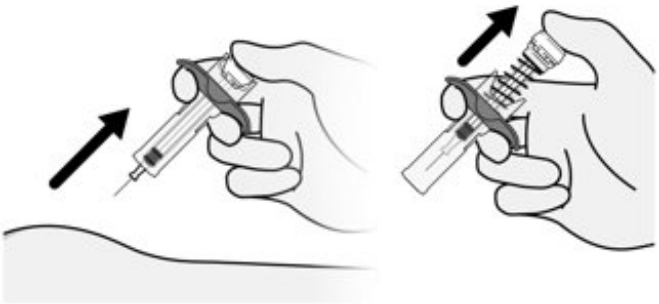


Figure I

Pull the Syringe away from the injection site, then release your thumb from

the plunger. The needle will retract and the Needle Safety Feature will cover the needle (See Figure I).
Caution: If the needle did not retract or you do not think you received the full dose, contact your healthcare provider for assistance.
If the needle does not retract, carefully place the Syringe into a sharps or puncture resistant container to avoid injury.

- There may be a small amount of liquid on the injection site. This is normal. If slight bleeding occurs from the injection site, press a gauze pad or cotton ball lightly against the site for a few seconds.
- **Do not** rub the injection site.

Dispose of the HULIO Syringe and Needle Cap
Put the used Syringe and Needle Cap in an FDA-cleared sharps disposal container or puncture resistant container right away to avoid injury (See “How should I throw away (dispose of) the used HULIO Prefilled Syringe and Needle Cap?” in Step 6).
Syringe is for single-dose only.
Do not reuse the Syringe even if all of the medicine was not injected.
Do not try to recap the needle as it could lead to a needle stick injury.

Step 6

How should I throw away (dispose of) the used HULIO Prefilled Syringe and Needle Cap?

- **Put your used Syringe and Needle Cap in an FDA-cleared sharps disposal container right away after use.**
- **Do not throw away (dispose of) Syringe or Needle Cap in your household trash.**

If you do not have an 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.
Do not recycle your used sharps disposal container.

Step 7

Write down the date you received your injection and the injection site used in the injection diary.

Injection Diary

Date	Injection Site Used

Customer Service
For Questions or Assistance,
Call Mylan at 1-877-446-3679 (1-877-4-INFO-RX)

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The Hulio Logo is a trademark of BGP Products Operations GmbH, a Viatris Company.

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Manufactured by:

Mylan Pharmaceuticals Inc.

Morgantown, WV 26505 U.S.A.

Manufactured for:

Mylan Specialty L.P.

Morgantown, WV 26505 U.S.A.

U.S. License No. 2210

Product of Japan

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

Revised: 11/2022
PCI:ADAL:IFUS:RX5

697925

PRINCIPAL DISPLAY PANEL – 20 mg/0.4 mL Syringe

Hulio®

(adalimumab-fkjp) injection

20 mg/0.4 mL Syringe

FOR SUBCUTANEOUS USE ONLY

ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide.

The entire carton is to be dispensed as a unit.
Return to pharmacy if dose tray seal is broken or missing.

2 Single-Dose
Prefilled Syringes

NDC 49502-381-02
Rx only

29 Gauge Needle

This carton contains:

- 2 dose trays (each containing 1 single-dose prefilled syringe with 29 gauge 1/2 inch length fixed needle)
- 2 alcohol preps
- 1 Quick Reference Guide
- 1 Instructions for Use
- 1 Medication Guide
- 1 Prescribing Information

Each 0.4 mL single-dose prefilled syringe contains 20 mg of adalimumab-fkjp, methionine (0.30 mg), monosodium glutamate (0.75 mg), polysorbate 80 (0.40 mg), sorbitol (19.1 mg) and Water for Injection, USP. Hydrochloric acid is added as necessary to adjust pH.

Contains no preservatives.

No U.S. standard of potency.

Prefilled syringe is for one time use only.

Dosage: See Prescribing Information.

Do not use beyond the expiration date.

Store in carton until time of administration with protection from light.

Store in refrigerator at 36°F to 46°F (2°C to 8°C).

A HULIO prefilled syringe may be stored at room temperature up to a maximum of 77°F (25°C) for up to 14 days with protection from light.

DO NOT FREEZE.

Manufactured by: **Mylan Pharmaceuticals Inc.**
Morgantown, WV 26505 U.S.A.

Manufactured for: **Mylan Specialty L.P.**
Morgantown, WV 26505 U.S.A.

U.S. License No. 2210
Product of Japan

Mylan.com

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PCI:381:2C:R1

PRINCIPAL DISPLAY PANEL – 40 mg/0.8 mL Syringe

Hulio®

(adalimumab-fkjp) injection

40 mg/0.8 mL Syringe

FOR SUBCUTANEOUS USE ONLY

ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide.

The entire carton is to be dispensed as a unit.
Return to pharmacy if dose tray seal is broken or missing.

2 Single-Dose
Prefilled Syringes

NDC 49502-382-02
Rx only

29 Gauge Needle

This carton contains:

- 2 dose trays (each containing 1 single-dose prefilled syringe with 29 gauge 1/2 inch length fixed needle)
- 2 alcohol preps
- 1 Quick Reference Guide
- 1 Instructions for Use
- 1 Medication Guide
- 1 Prescribing Information

Each 0.8 mL single-dose prefilled syringe contains 40 mg of adalimumab-fkjp, methionine (0.60 mg), monosodium glutamate (1.50 mg), polysorbate 80 (0.80 mg), sorbitol (38.2 mg) and Water for Injection, USP. Hydrochloric acid is added as necessary to adjust pH.

Contains no preservatives.

No U.S. standard of potency.

Prefilled syringe is for one time use only.

Dosage: See Prescribing Information.

Do not use beyond the expiration date.

Store in carton until time of administration with protection from light.

Store in refrigerator at 36°F to 46°F (2°C to 8°C).

A HULIO prefilled syringe may be stored at room temperature up to a maximum of 77°F (25°C) for up to 14 days with protection from light.

DO NOT FREEZE.

Manufactured by: **Mylan Pharmaceuticals Inc.**

Morgantown, WV 26505 U.S.A.

Manufactured for: **Mylan Specialty L.P.**
Morgantown, WV 26505 U.S.A.

U.S. License No. 2210
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Mylan.com

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PCI:382:2C:R2

725664

PRINCIPAL DISPLAY PANEL – 40 mg/0.8 mL Pen

Hulio® Pen

(adalimumab-fkjp) injection

40 mg/0.8 mL

FOR SUBCUTANEOUS USE ONLY

ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide.

The entire carton is to be dispensed as a unit.
Return to pharmacy if dose tray seal is broken or missing.

NDC 49502-382-02
Rx only

29 Gauge Needle

This carton contains:

- 2 dose trays (each containing 1 single-dose prefilled syringe with 29 gauge 1/2 inch length fixed needle)
- 2 alcohol preps
- 1 Quick Reference Guide
- 1 Instructions for Use
- 1 Medication Guide
- 1 Prescribing Information

2 Single-Dose Prefilled Pens

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The Hulio Logo is a trademark of BGP Products Operations GmbH, a Viatris Company.

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Each 0.8 mL single-dose prefilled pen contains 40 mg of adalimumab-fkjp, methionine (0.60 mg), monosodium glutamate (1.50 mg), polysorbate 80 (0.80 mg), sorbitol (38.2 mg) and Water for Injection, USP. Hydrochloric acid is added as necessary to adjust pH.

Contains no preservatives.

No U.S. standard of potency.

Prefilled pen is for one time use only.

Dosage: See Prescribing Information.

Do not use beyond the expiration date.

Store in carton until time of administration
with protection from light.

Store in refrigerator at 36°F to 46°F (2°C to 8°C).

A HULIO prefilled Pen may be stored at room
temperature up to a maximum of 77°F (25°C)
for up to 14 days with protection from light.

DO NOT FREEZE.

Manufactured by:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Manufactured for:
Mylan Specialty L.P.
Morgantown, WV 26505 U.S.A.

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Mylan.com

PCI:380:2C:R2

725661

HULIO

adalimumab kit

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:49502-381

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:49502-381-02	2 in 1 KIT	07/01/2023	
1		1 in 1 TRAY; Type 0: Not a Combination Product		

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	5 SYRINGE	2 mL
Part 2	2 PACKET	2 mL

Part 1 of 2

HULIO

adalimumab injection, solution

Product Information

Item Code (Source)	NDC:49502-567
Route of Administration	SUBCUTANEOUS

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ADALIMUMAB (UNII: FYS6T7F842) (ADALIMUMAB - UNII:FYS6T7F842)	ADALIMUMAB	20 mg in 0.4 mL

Inactive Ingredients

Ingredient Name	Strength
METHIONINE (UNII: AE28F7PNPL)	0.30 mg in 0.4 mL
MONOSODIUM GLUTAMATE (UNII: W81N5U6R6U)	0.75 mg in 0.4 mL
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	0.40 mg in 0.4 mL
SORBITOL (UNII: 506T60A25R)	19.1 mg in 0.4 mL
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:49502-567-06	2 in 1 KIT		
1		1 in 1 TRAY		
1		0.4 mL in 1 SYRINGE; Type 3: Prefilled Biologic Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA761154	07/01/2023	

Part 2 of 2

ALCOHOL
isopropyl swab

Product Information

Item Code (Source)	NDC:49502-569
Route of Administration	TOPICAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ISOPROPYL ALCOHOL (UNII: ND2M416302) (ISOPROPYL ALCOHOL - UNII:ND2M416302)	ISOPROPYL ALCOHOL	0.70 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:49502-569-02	2 in 1 KIT		
1		1 mL in 1 PACKET; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA761154	07/01/2023	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA761154	07/01/2023	

HULIO
adalimumab kit

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:49502-382

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:49502-382-02	2 in 1 KIT	07/01/2023	
1		1 in 1 TRAY; Type 0: Not a Combination Product		

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	3 SYRINGE	2 mL
Part 2	2 PACKET	2 mL

Part 1 of 2

HULIO

adalimumab injection, solution

Product Information

Item Code (Source)	NDC:49502-554
Route of Administration	SUBCUTANEOUS

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ADALIMUMAB (UNII: FYS6T7F842) (ADALIMUMAB - UNII:FYS6T7F842)	ADALIMUMAB	40 mg in 0.8 mL

Inactive Ingredients

Ingredient Name	Strength
METHIONINE (UNII: AE28F7PNPL)	0.60 mg in 0.8 mL
MONOSODIUM GLUTAMATE (UNII: W81N5U6R6U)	1.50 mg in 0.8 mL
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	0.80 mg in 0.8 mL
SORBITOL (UNII: 506T60A25R)	38.2 mg in 0.8 mL
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:49502-554-06	2 in 1 KIT		

1		1 in 1 TRAY		
1		0.8 mL in 1 SYRINGE; Type 3: Prefilled Biologic Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA761154	07/01/2023	

Part 2 of 2

ALCOHOL

isopropyl swab

Product Information

Item Code (Source)	NDC:49502-556
Route of Administration	TOPICAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ISOPROPYL ALCOHOL (UNII: ND2M416302) (ISOPROPYL ALCOHOL - UNII:ND2M416302)	ISOPROPYL ALCOHOL	0.70 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:49502-556-06	2 in 1 KIT		
1		1 mL in 1 PACKET; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA761154	07/01/2023	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA761154	07/01/2023	

HULIO

adalimumab kit

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:49502-380

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:49502-380-02	2 in 1 KIT	07/01/2023	
1		1 in 1 TRAY; Type 0: Not a Combination Product		

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	3 SYRINGE	2 mL
Part 2	2 PACKET	2 mL

Part 1 of 2

HULIO

adalimumab injection, solution

Product Information

Item Code (Source)	NDC:49502-540
Route of Administration	SUBCUTANEOUS

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ADALIMUMAB (UNII: FYS6T7F842) (ADALIMUMAB - UNII:FYS6T7F842)	ADALIMUMAB	40 mg in 0.8 mL

Inactive Ingredients

Ingredient Name	Strength
METHIONINE (UNII: AE28F7PNPL)	0.60 mg in 0.8 mL
MONOSODIUM GLUTAMATE (UNII: W81N5U6R6U)	1.50 mg in 0.8 mL
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	0.80 mg in 0.8 mL
SORBITOL (UNII: 506T60A25R)	38.2 mg in 0.8 mL
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:49502-540-06	2 in 1 KIT		
1		1 in 1 TRAY		
1		0.8 mL in 1 SYRINGE; Type 3: Prefilled Biologic Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA761154	07/01/2023	

Part 2 of 2

ALCOHOL

isopropyl swab

Product Information

Item Code (Source)	NDC:49502-542
Route of Administration	TOPICAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ISOPROPYL ALCOHOL (UNII: ND2M416302) (ISOPROPYL ALCOHOL - UNII:ND2M416302)	ISOPROPYL ALCOHOL	0.70 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:49502-542-06	2 in 1 KIT		
1		1 mL in 1 PACKET; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA761154	07/01/2023	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA761154	07/01/2023	

Labeler - Mylan Specialty L.P. (194775557)

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