

HUMIRA[®] **(adalimumab)**

Safety **MONOGRAPH**

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1.0 INTRODUCTION

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences. Adalimumab binds with high affinity and specificity to tumor necrosis factor (TNF- α), a cytokine known to direct the inflammatory response in many tissues involved in autoimmune diseases.

TNF inhibitors, including adalimumab, have offered significant benefits to many patients. Adalimumab has an established well described safety profile based on more than 15 years of clinical trial experience and over 10 years of postmarketing surveillance.

The purpose of this safety monograph is to provide physicians and other health care professionals with the following:

1. Information about the key identified safety risks patients may encounter during treatment with TNF inhibitors therapy, including adalimumab (Humira®);
2. Ways to manage or reduce these identified safety risks through screening and monitoring of patients while they are receiving TNF inhibitor therapy;
3. Aid healthcare professionals in counseling patients about the risks of TNF antagonist therapy and the importance of timely reporting of any relevant signs or symptoms.

This safety monograph is one component of an adalimumab safety education program AbbVie has initiated for healthcare professionals (HCPs).

2.0 KEY KNOWN SAFETY RISKS OF TNF INHIBITOR THERAPY

The next sections detail the risk for infections, malignancy, heart failure, and demyelinating diseases which have been identified in adalimumab labels throughout the world. These risks are common to all products that belong to the TNF inhibitor class of therapies. These risks can be found in a prominent position in the label.

2.1 Infections and Serious Infections

Serious infections have been reported in patients receiving TNF-inhibitors, including adalimumab. The causes of these infections include bacterial, mycobacterial, invasive fungal (disseminated or extrapulmonary histoplasmosis, aspergillosis, coccidioidomycosis) viral, parasitic, or other opportunistic infectious agents. Rare cases of tuberculosis (TB), listeriosis, Legionellosis, pneumocystosis, and candidiasis other than oral thrush have also been reported. Types of serious infections seen in clinical trials included pneumonia, pyelonephritis, septic arthritis, sepsis, and septicemia. Hospitalization or fatal outcomes associated with infections have also been reported.

Patients greater than 65 years of age, with comorbid conditions, and/or taking concomitant immunosuppressants, such as corticosteroids or methotrexate [MTX], may be at greater risk of infection of all types. Some infections are only encountered in certain geographic areas. Therefore, the type of infection can vary by where the patient lives or where they have traveled.

Adalimumab therapy should not be initiated in patients with an active infection, including localized infections or common infections, such as a cold or the flu.

Tuberculosis and other opportunistic infections are discussed in detail in Section 2.1.1 and Section 2.1.2.

In order to minimize the risk of serious infections during adalimumab therapy:

- > Patients and physicians should monitor closely for infections, including tuberculosis before, during, and after treatment with adalimumab. The elimination of adalimumab from the body may take up to four months; therefore, monitoring should be continued for 4 months after adalimumab is stopped.
- > Physicians should be aware that some patients who have been successfully treated for active tuberculosis have been reinfected with tuberculosis while being treated with adalimumab.
- > Patients who develop a new infection while undergoing treatment with adalimumab should be monitored closely and undergo a complete diagnostic evaluation since infections may present in an unexpected way, such as an uncommon location for that infection in the body.
- > There may be a need to suspend adalimumab treatment before surgery.
- > Administration of adalimumab should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled.
- > For patients who develop signs and symptoms such as fever, malaise, weight loss, sweats, cough, dyspnea, and/or pulmonary infiltrates or other evidence of a serious systemic illness with or without concomitant septic shock, an invasive fungal infection should be suspected and administration of adalimumab should be promptly discontinued. Diagnosis and administration of empiric antifungal therapy should be made in consultation with a physician with expertise in the care of patients with invasive fungal infections.
- > Patients treated with adalimumab may receive concurrent vaccinations, except those using live viruses.

2.0 KEY KNOWN SAFETY RISKS OF TNF INHIBITOR THERAPY

Serious Infections – Frequently Asked Questions

1. What are the risks of developing a serious infection as a result of biologic treatment?
2. What happens if a patient treated with a TNF inhibitor develops a serious infection?
3. Does the risk of infections in TNF inhibitor-treated patients increase over time?
4. How long before surgery should a patient discontinue TNF inhibitor therapy?
5. Is there an increase in infections at the surgical site in peri-operative use of biologics?

1. What are the risks of developing a serious infection as a result of biologic treatment?

A serious infection is defined as an infection requiring either intravenous antibiotic use or hospitalization, or one that involved death.

Most patients receiving adalimumab who developed infections may have been taking concomitant immunosuppressants such as methotrexate, thiopurines (i.e., azathioprine and 6-mercaptopurine), or corticosteroids, which may also increase the risk of infection.

Patients over the age of 65 years will have a greater risk of infection than younger patients. Galloway et al. (2011) showed that increasing age was an independent risk factor for serious infections on disease-modifying anti-rheumatic drugs (DMARDs) as well as TNF inhibitors.

The autoimmune diseases that are treated by TNF inhibitors have inherent risks of infection as well. For instance, the incidence of serious infections in patients with rheumatoid arthritis (RA) is increased relative to the general population and those individuals without RA. There are no significant differences in infection risk associated with adalimumab therapy that are unique to an indication. The difference in rates of infection among indications appears to be based mostly on the contribution to the risk from the underlying disease being treated.

For example, patients with inflammatory bowel disease (IBD) taking adalimumab have more gastrointestinal infections than patients who take adalimumab for psoriasis.

The article published by Burmester et al. 2013 provided infection incidence rates for the adalimumab controlled clinical trials through 06 November 2010. Incidence rates of serious infections in adalimumab-treated subjects are comparable to the rates of serious infection in the disease populations studied that were not necessarily treated with TNF inhibitors. From adalimumab clinical trial data, the RA subject rate of infections was 4.6 E/100 PYs, while the Crohn's disease (CD) patient rate was 6.7 E/100PYs. (Burmester 2013) These rates apply to a population. A specific individual may have a greater or lesser risk. The rates are expressed this way because not only does the individual duration of product treatment matter, but in a population, the number of patients included to create that rate makes a difference. A patient-year is defined as one patient on therapy continually for one year.

The most serious infections experienced by RA patients were respiratory tract infections. CD patients in clinical trials most commonly experienced gastrointestinal abscess, a frequent complication of the underlying bowel disease. The second most serious infections in CD patients were pulmonary infections.

2. What happens if a patient on a TNF inhibitor develops a serious infection?

Serious infections are discussed in Section 2.1 of this document.

Adalimumab should be discontinued if a patient develops a serious infection.

If a patient presents with fever and cough, and especially if systemic symptoms are present, they should receive a full work-up for evidence of an opportunistic infection. Look for infections such as TB or those having a fungal cause. Ask about recent travel or exposure to other people with infection. Seek consultation with an infectious disease specialist if possible, since empiric anti-fungal therapy may be indicated in these patients.

AbbVie does not have a recommendation regarding an appropriate amount of time for interruption of adalimumab therapy after the development of an infection. This is a decision best made by the treating physician based on clinical course and the patient's response and prognosis following treatment for the infection.

2.0 KEY KNOWN SAFETY RISKS OF TNF INHIBITOR THERAPY

3. Does the risk of infections in TNF inhibitor-treated patients increase over time?

Information about the incidence of infections after long term administration of TNF inhibitor therapy is limited. However, there are data to suggest that the risk of infections in patients treated with TNF inhibitors may vary depending on the stage of treatment, that is, risk may be different early after therapy starts compared to after a lengthy period of treatment. Some studies suggested that the risk of infection is higher early after therapy begins. In an observational registry of over 11, 700 RA patients in the United Kingdom (British Society for Rheumatology Biologics Register [BSRBR]), the risk of serious infections was highest during the first 6 months of TNF inhibitor therapy. (Galloway 2011) However, a recently completed open label adalimumab trial of RA patients that spanned 10 years suggested that the risk is similar throughout therapy.

4. How long before surgery should a patient discontinue TNF inhibitor therapy?

AbbVie does not have a recommendation regarding whether to discontinue adalimumab therapy prior to an elective surgical procedure or a recommendation regarding the optimal time of therapy interruption. Obviously, therapy interruption is not an option in emergency situations. One should keep in mind that the longest half-life measured during trials suggests adalimumab is not completely eliminated for up to 70 days (5 half-lives) following the last dose. The average half-life is much shorter than the longest half-life and suggests that the published guidelines, summarized below, may be applied. The recommendation for the length of the waiting period ranges from no waiting time up to a month off of therapy, depending on the guidance:

- > According to the ACR recommendations for the use of nonbiologic and biologic DMARDs in RA, biologic DMARDs should not be used for at least 1 week prior to and 1 week after surgery with consideration given to the pharmacokinetic properties of the individual biologic agent and the infectious risk of the surgery. (Singh 2012)

- > The European Crohn's and Colitis Organisation (ECCO) guidelines (Dignass 2010) indicate that "There is no consensus among experts as to the optimal time between treatment with a TNF inhibitor and abdominal surgery, with equal proportions suggesting one month, a longer period, or that it does not matter. There is no evidence from the literature in this regard."
- > According to American College of Gastroenterology (ACG) guidelines, (Lichtenstein 2009) "The peri-operative use of azathioprine or 6-mercaptopurine, and/or infliximab has not been demonstrated to be a risk factor for postoperative infectious complications, in contrast to corticosteroids that do increase the risk of postoperative infectious complications."
- > According to British Society of Rheumatology (BSR) guidelines (Ledingham 2005), "Treatment with infliximab, etanercept and adalimumab should be withheld for 2 to 4 weeks prior to major surgical procedures. Treatment may be restarted post-operatively if there is no evidence of infection and once wound healing is satisfactory (information provided by the drug companies)."

5. Is there an increase in infections at the surgical site in peri-operative use of biologics?

Limited data are available about whether there is an increase in the risk of infection at the surgical sites associated with peri-operative use of biologics. Retrospective studies and a retrospective chart review evaluated the peri-operative use of TNF inhibitors, including adalimumab, in patients with RA and in a patient with psoriatic arthritis. (Greenberg 2010; Bergstrom 2004; Smitten 2008) Unfortunately, the patient outcomes were inconsistent among these studies and, as a result, specific guidance about post operative infection rate and wound healing cannot be provided.

2.0 KEY KNOWN SAFETY RISKS OF TNF INHIBITOR THERAPY

2.1.1 Tuberculosis (TB)

Tuberculosis (TB) including reactivation of latent TB and new onset of TB infection, has been reported in patients receiving TNF inhibitors, including adalimumab. These reports included pulmonary and extrapulmonary (i.e., disseminated) TB.

TNF- α plays an important role in protection against murine *Mycobacterium tuberculosis* infection. (Flynn 1995) In vitro and in vivo studies in mice demonstrated that TNF- α provides protective mechanisms in macrophages against *M. tuberculosis*. The studies further show that the absence of TNF- α has a detrimental effect on the ability of granulomas to contain and restrict the replication of tubercle bacilli. TNF inhibitors may play a role in inhibiting the maturation of phagosomes in human macrophages (Harris 2008) as well as decreasing CD8+ T-cells, (Bruns 2009) both of which are needed for antimicrobial activity against *M. tuberculosis*. Therefore, given the importance of TNF- α in protection against non-necrotizing infections like TB, patients with prior TB exposure or infection, even treated infection, should be closely monitored for the appearance of active infection while receiving a TNF inhibitor.

To minimize the risk of TB, all patients must be evaluated for evidence of active or inactive (“latent”) tuberculosis infection prior to treatment with adalimumab:

- > A detailed medical history of tuberculosis exposure or infection and previous and/or current immunosuppressive therapies should be collected. Appropriate screening tests (i.e. tuberculin skin test, interferon-gamma release assays, and chest x-ray) should be performed using local recommendations or guidance from other sources, such as the CDC or WHO. Record the date and results of these tests in the patient chart and the patient information card for the patient to keep.
- > There is a risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised. Repeat TB testing at intervals during TNF inhibitor therapy may help identify TB infection in patients who have a negative test(s) before treatment begins.
- > If active tuberculosis is diagnosed, adalimumab therapy must not be initiated.
- > If latent tuberculosis is suspected, consult a physician with expertise in the treatment of tuberculosis.
- > If latent tuberculosis is diagnosed, appropriate anti-tuberculosis prophylaxis treatment should be started before the initiation of adalimumab, and in accordance with local recommendations.
- > Consider starting anti-tuberculosis prophylaxis treatment before the initiation of adalimumab in patients with risk factors for tuberculosis despite a negative test for tuberculosis. This would include patients with a history of latent or active tuberculosis who cannot confirm that they received an adequate course of treatment.
- > Carefully consider the risk and benefit of adalimumab therapy in patients who have been exposed to tuberculosis or who have traveled in areas of high risk for tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis.
- > Patients should be instructed to seek medical advice if signs/symptoms suggestive of a tuberculosis infection (e.g. persistent cough, wasting/weight loss, low grade fever, listlessness) occur at any time during therapy or even after therapy with adalimumab has been stopped.

2.0 KEY KNOWN SAFETY RISKS OF TNF INHIBITOR THERAPY

Tuberculosis – Frequently Asked Questions

1. How do you manage a patient who develops active TB while undergoing treatment with a biologic?
2. How do you manage a patient who is diagnosed with latent TB infections while undergoing treatment with a biologic?
3. Is it safe to start a patient who has a negative chest x-ray but a positive Tuberculin skin test on a TNF inhibitor?
4. Can a patient with a history of TB be treated with a biologic?

1. How do you manage a patient who develops active TB while undergoing treatment with a biologic?

The risk of TB with TNF inhibitor therapy is discussed in Section 2.1.1 of this document. Adalimumab should be discontinued if a patient develops active tuberculosis. Anti-tuberculosis therapy (as per local guidelines) should be initiated immediately upon diagnosis of TB and the patient should be closely monitored with regular follow-up.

Refer to local/regional TB guidelines or the international guidelines listed at the end of this section of this document.

2. How do you manage a patient who is diagnosed with latent TB infection who develops active TB infection while undergoing treatment with a biologic?

Adalimumab should be discontinued if a patient develops active tuberculosis. Patients with latent TB infection who develop active TB should be referred to a TB specialist for initiation of anti-TB therapy. In patients with latent TB infection, without active TB, adalimumab treatment can be continued during TB prophylaxis treatment.

3. Is it safe to start an asymptomatic patient who has a negative chest x-ray but a positive Tuberculin skin test on a TNF inhibitor?

First of all, active TB must be excluded in a patient like this. While the chest x-ray may appear normal, TB may be present in other sites in the body. If any signs or symptoms of TB and/or extrapulmonary TB disease are found, a careful investigation should be conducted. If active TB is diagnosed, adalimumab must not be initiated.

The presence of a positive tuberculin skin test (induration ≥ 5 mm) with a normal chest x-ray and no other relevant signs or symptoms indicates that the patient has latent TB. TB prophylaxis must be initiated before starting a TNF inhibitor in this situation.

There are no studies that provide guidance about when to start a TNF inhibitor in a patient receiving TB prophylaxis. Expert opinion, however, recommends starting 4 weeks after the initiation of TB prophylaxis.

AbbVie recommends consultation with a physician with expertise in the treatment of TB to aid in the decision and management of these patients.

4. Can a patient with a history of TB be treated with a biologic?

These patients may be treated with a biologic following a consideration of the benefit-risk for the individual patient. Keep in mind, active TB has developed in patients receiving adalimumab whose screening results for latent tuberculosis were negative, and some patients who have previously received treatment for latent or active TB have developed active tuberculosis while being treated with TNF inhibitor agents. If the decision is made to treat a patient who has a history of TB, they should be monitored for signs and symptoms of active tuberculosis, including the appearance of TB in sites other than the lungs.

If the patient has completed TB treatment at some point in the past, the risk for reactivation is low. If TB treatment has not been completed, consultation with a TB specialist is recommended in order to evaluate whether to restart the TB treatment or start TB prophylaxis (as per local guidelines) prior to initiation of adalimumab therapy. (Perez 2005) Patients should be closely monitored for the development of signs and symptoms of TB and other infections during and after treatment with adalimumab. (Saag 2008; Doherty 2008)

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2.1.2 Opportunistic Infections

Patients taking TNF inhibitors are more susceptible to serious fungal infections, such as histoplasmosis, coccidioidomycosis, blastomycosis, aspergillosis, systemic candidiasis, and other opportunistic infections. These infections have not been consistently recognized by health care professionals in patients taking TNF inhibitors because of their often unusual presentation and sometimes because the patient is treated empirically with antibiotics without further evaluation. These situations have resulted in delays in appropriate treatment, some of which have resulted in fatal outcomes.

Histoplasma capsulatum, the fungus that causes histoplasmosis, is highly endemic in several parts of the world, including the regions of the Ohio and Mississippi River valleys of the United States. (Lee 2002) It has also been seen in the northern parts of New York and Vermont. Individuals may acquire histoplasmosis after inhalation of tiny fragments of *H. capsulatum* that are released into the air after contaminated soil is disrupted (i.e., construction sites). In general, immunocompetent individuals infected with *H. capsulatum* do not exhibit symptoms, and the infection is self-limited. However, immunocompromised patients infected with *H. capsulatum* have a high risk of presenting with clinically apparent symptoms.

Aspergillus is a ubiquitous mold that exists in soil, water, decaying vegetation, moldy hay or straw, and organic debris. (Carver 2008) Individuals may acquire aspergillosis after inhalation of spores of the fungi. Usually this does not result in infection, however, even in healthy persons, inhalation of large amounts of aspergillosis is sufficient to cause disease. Invasion of lung tissue is usually limited to immunosuppressed patients. Patients who are more susceptible to *Aspergillus* infection have prior pulmonary disease, including pneumonia and chronic obstructive pulmonary disease.

Blastomyces dermatitidis, the fungi that cause blastomycosis, grow as microfoci in warm, moist soil of wooded areas rich in organic debris. (Chapman 2008) Blastomycosis is endemic in several different parts of the world, including the Southeastern and South central states bordering the Mississippi and Ohio River basins, the Midwestern states, Canadian provinces bordering the Great Lakes, and a small area in New York and Canada along the St. Lawrence River.

It has also been frequently reported in Africa. Blastomycosis is a systemic pyogranulomatous infection that arises after inhalation of *Blastomyces dermatitidis* spores and primarily involves the lungs. Any organ can be infected, although extrapulmonary disease of the skin, bones and genitourinary system is most common. Presentation of pulmonary blastomycosis can range from acute or chronic pneumonia, as well as an asymptomatic infection, with hematogenous spread occurring frequently.

Candida, the fungi that cause candidosis (candidiasis), naturally exists as a part of the microflora of the gastrointestinal tract and can act as part of the vaginal flora. (Brown 2008) Greater than 150 species of *Candida* exist, however those considered clinically important pathogens in human disease include *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. krusei*, *C. stellatoidea*, *C. guilliermondi*, *C. lusitaniae*, and *C. glabrata*. (Carver 2008) Although the virulence among *Candida* species varies, the presence of *Candida* in most healthy adults generally stimulates antibody formation and cell-mediated immunity without leading to clinically apparent symptoms of infection. (Brown 2008) However, impairment of a human's host defenses is generally the reason why *Candida* changes from a commensal to pathogenic role. The majority of oral fungal infections are caused by *Candida*, and oropharyngeal candidiasis may predispose patients to develop more invasive disease, including esophageal candidiasis, if left untreated.

Coccidioidomycosis immitis, the fungi that cause coccidioidomycosis, is found in the arid regions of the United States, Mexico, Central America, and South America. (Ampel 2008) Individuals may acquire coccidioidomycosis after inhalation of windborne arthrospores from soil sites. Most cases are subclinical and the infection is self-limited. However, the immunocompromised patient infected by this pathogen is at a greater risk for developing disseminated disease.

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Legionella is the genus of bacteria that cause the two clinical syndromes (Legionnaires' disease and Pontiac fever) referred to as Legionellosis. (Sabria 2008) Legionnaires' disease is pneumonia caused by *Legionella* and Pontiac fever is linked to *Legionella* species and typically presents as an acute, flu-like illness, which is self-limited and does not include pneumonia. The family Legionellaceae includes more than 49 species with more than 64 serogroups. *Legionella pneumophila* causes 80-90% of human infections. The natural habitat of *Legionella* is water. Colonization of residential and industrial water supplies, including potable-water distribution systems in hospitals, long term-care facilities, hotels, and large buildings, has been linked to community-acquired Legionnaires' disease. Aerosolization, aspiration, and direct instillation into lungs are some of the modes of transmission of *Legionella*. Therapies, including treatment with glucocorticoids or TNF inhibitors, have been identified as risk factors for Legionnaires' disease. Immunosuppressed patients who do not receive appropriate treatment early in the course of the infection have mortality rates as high as 80%.

Listeria monocytogenes, the bacterium that causes listeriosis, is not a common cause of illness in the general population. (Lorber 2009) However, in immunosuppressed patients, neonates, pregnant women, and others with impaired cell-mediated immunity, it may cause life-threatening illness. *L. monocytogenes* is found in soil, decaying vegetation, water, and as part of the fecal flora of many mammals. Many foods can be contaminated with *L. monocytogenes* and most human listeriosis appears to be foodborne.

Pneumocystis is a fungus of low virulence found in the lungs of humans and is a cause of pneumonia in immunocompromised hosts. (Walzer 2009) An important predisposing factor in the development of pneumocystosis is impaired cellular immunity, most evident by the development of pneumocystosis in HIV-infected patients, but also occurring in patients receiving immunosuppressive drug therapy.

In order to minimize the risk of opportunistic infections in patients taking adalimumab:

- > Adalimumab must not be initiated in patients who have severe infections, including opportunistic infections.
- > Patients who develop a new opportunistic infection while undergoing treatment with adalimumab should discontinue adalimumab, be monitored closely, and undergo a complete diagnostic evaluation for appropriate therapy until the infection is controlled.
- > An invasive fungal infection should be suspected and administration of adalimumab should be promptly discontinued in patients who develop signs and symptoms, such as fever, malaise, weight loss, sweats, cough, dyspnoea, and/or pulmonary infiltrates or other serious systemic illness with or without concomitant shock. Diagnosis and administration of empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the care of patients with invasive fungal infections.

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2.1.3 Hepatitis B Reactivation

Use of TNF inhibitors has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF inhibitor 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.

TNF- α interferes with viral replication and is essential for stimulating HBV-specific T-cell responses. (Herbein 2000; Kasahara 2003) As such, TNF inhibition could interfere with the clearing of the HBV from infected hepatocytes and permit the virus to escape the host's immune defense. (Nathan 2006)

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 inhibitor therapy to prevent HBV reactivation.

In order to minimize the risk of HBV reactivation in patients taking adalimumab:

- > Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF inhibitor therapy.
- > Prescribers should exercise caution in prescribing TNF inhibitors to patients identified as carriers of HBV.
- > Patients who are carriers of HBV and require treatment with TNF inhibitors should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.
- > In patients who develop HBV reactivation, adalimumab should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

2.2 Malignancies

Malignancies, including lymphoma, non-melanoma skin cancer, melanoma, leukemia, hepatosplenic T-cell lymphoma, and Merkel cell carcinoma (MCC; neuroendocrine carcinoma of the skin), have been reported in patients receiving treatment with TNF inhibitors.

During the long-term open label trials with adalimumab, the overall rate of malignancies was similar to what would be expected for an age, gender and race-matched general population. With current knowledge, a possible risk for the development of lymphomas or other malignancies in patients treated with a TNF inhibitor cannot be excluded.

In the controlled portions of clinical trials of some TNF inhibitors, including adalimumab, more cases of lymphoma and other malignancies have been observed among TNF inhibitor-treated adult patients compared to control-treated adult patients. Furthermore, there is an increased background lymphoma risk in RA patients with long-standing, highly active, inflammatory disease, which complicates risk estimation. In 47 global controlled and uncontrolled clinical trials of adalimumab in adult patients with RA, psoriatic arthritis (PsA), ankylosing spondylitis (AS), CD, ulcerative colitis (UC), and psoriasis (Ps), the most frequently observed malignancies, other than lymphoma and non-melanoma skin cancers (NMSCs), were breast, colon, prostate, and lung cancer, and melanoma. However, the size of the control groups and limited duration of the controlled portions of studies precludes the ability to draw firm conclusions about the risk.

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 US population according to the National Cancer Institute's (NCI's) Surveillance, Epidemiology, and End Results (SEER) database (adjusted for age, gender, and race).

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Postmarketing cases of acute leukemia, chronic leukemia, and MCC have also been reported in association with TNF inhibitor use. 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 exposure.

MCC is a rare, aggressive skin cancer which is often unrecognized because of its benign appearance. Therefore, this skin cancer tends to be diagnosed after metastatic lesions are present. The frequency of MCC is strongly related to age, as the disease is extremely rare in people under the age of 50 years. The incidence of MCC increases with increasing age, reaching the maximum for the oldest age category (85+ years of age). In addition, immunosuppression is a well recognized risk factor for the development of MCC, particularly in the setting of HIV infection, chronic lymphocytic leukemia, organ transplantation (use of anti-rejection drugs), and autoimmune disorders, including RA and CD. (Dinh 2007) Although there is no clear evidence of adalimumab therapy involvement in MCC appearance, it is important to warn of the possible risk of MCC to prescribing physicians as well as patients.

According to the American College of Rheumatology recommendations for the use of DMARDs and biologic agents in the treatment of RA, any biologic agent may be started or resumed in patients who have had a treated solid malignancy or a treated NMSC > 5 years in the past who would otherwise qualify for the treatment of RA. (Singh 2012)

The Assessment of Spondyloarthritis International Society handbook states that the use of TNF inhibitors is contraindicated in patients with a history of malignancy, with the exceptions of basal cell carcinoma and malignancies diagnosed and treated > 10 years previously in which the probability of complete cure is very high. (Sieper 2009)

However, analysis of data gathered from the British Society for Rheumatology Biologics Register (BSRBR), a registry of RA patients in the UK, analyzing the influence of TNF inhibitor treatment on cancer incidence in RA patients with a history of malignancy indicate that the incidence of malignancies in such patients was not increased compared to RA patients with prior malignancy treated with traditional DMARDs. (Dixon 2010)

In order to minimize the risk of malignancies in patients taking adalimumab:

- > All patients, and in particular patients with a medical history of extensive immunosuppressant therapy or Ps patients with a history of psoralen + UV-A (PUVA) treatment, should be examined for the presence of non melanoma skin cancer prior to, and during, treatment with adalimumab.
- > Treatments with azathioprine or 6-mercaptopurine and adalimumab may potentially increase the risk of hepatosplenic T-cell lymphoma. Combination treatment of this type should be carefully considered, especially in patients with IBD (CD and UC).
- > Caution should be exercised when using any TNF inhibitor in patients with COPD, as well as any patients who have an increased risk of malignancy due to heavy smoking.
- > Caution should be exercised in considering adalimumab to treat patients with a history of malignancy or in continuing treatment of patients who develop a malignancy.
- > All patients with UC are at increased risk for colonic dysplasia or colon carcinoma. This includes those patients with longstanding UC or with primary sclerosing cholangitis and those with a history of dysplasia. UC patients are to be screened for dysplasia and colon cancer at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations. Current evidence does not provide evidence whether or not adalimumab treatment influences the risk for developing dysplasia or colon cancer in UC patients.

2.0 KEY KNOWN SAFETY RISKS OF TNF INHIBITOR THERAPY

2.2.1.1 Hepatosplenic T-cell Lymphoma (HSTCL)

Very rare postmarketing reports of hepatosplenic T-cell lymphoma (HSTCL) have been identified in patients treated with adalimumab. Most of the patients had prior infliximab therapy as well as concomitant or preceding azathioprine or 6-mercaptopurine use for IBD. The causal association of HSTCL with adalimumab has not been established. HSTCL is an extranodal and systemic neoplasm derived from cytotoxic T-cells (usually of gamma delta T-cell receptor type), demonstrating marked sinusoidal infiltration of spleen, liver, and bone marrow. (Weidmann 2000; Bernheim 2009; Belhadj 2003; Khan 2001; Zeidan 2007; Cooke 1996) This rare lymphoma type constitutes less than 5% of all peripheral T-cell neoplasms. (Mackey 2007; Thayu 2005; Navarro 2003) Of the fewer than 200 cases reported worldwide in the literature, the peak incidence appears to occur in adolescents and young adults, (Mackey 2009; Bernheim 2009; Cooke 1996; Khan 2001) and is more frequent in males than in females. (Weidmann 2000; Belhadj 2003; Cooke 1996; Khan 2001; Kraus 1998) Patients typically present with hepatosplenomegaly and type B symptoms (fever, night sweats, and weight loss), but no lymphadenopathy. (Belhadj 2003; Khan 2001; Kraus 1998; Zeidan 2007) Peripheral blood smear evaluation in patients with HSTCL may show anemia, thrombocytopenia, and circulating lymphoma cells. (Belhadj 2003; Khan 2001; Zeidan 2007) During the course of the disease, atypical T-cells diffusely infiltrate liver, spleen, bone marrow, and other organs, leading to various clinical manifestations and complications. (Weidmann 2000; Belhadj 2003; Khan 2001) The course of this disease is aggressive, (Belhadj 2003; Cooke 1996; Khan 2001; Kraus 1998) with the median survival estimated to be less than 2 years. (Belhadj 2003; Cooke 1996; Khan 2001)

2.2.1.2 Malignancies in Pediatric Populations

Lymphoma and other malignancies, some fatal, have been reported among children and adolescents who received treatment with TNF inhibitor agents, including adalimumab. 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. These malignancies occurred after a median of 30 months of therapy based on reported cases. 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 reports from health care professionals.

To date, no malignancies have been observed in 203 patients aged 2 to 17 years representing an exposure of 605.3 PYs during adalimumab trials in pediatric and adolescent patients with juvenile idiopathic arthritis (JIA). In addition, no malignancies have been observed in 192 pediatric patients representing an exposure of 258.9 PYs during an adalimumab trial in pediatric patients with CD.

Malignancies – Frequently Asked Questions

1. How do you manage patients with history of malignancy?
2. What do you do with a patient who requires a biologic who has had breast cancer in the last 5 years?
3. Can you start a TNF inhibitor in a patient who is currently being treated for cancer (breast cancer/lung cancer/other)?
4. Does TNF inhibitor therapy increase the risk of new cancers in patients with a prior history of malignancy?
5. Does the use of TNF inhibitor therapy increase the risk of skin cancer?
6. Does the use of a biologic increase the risk of recurring lymphoma in patients who have a prior history of lymphoma?
7. What do you do if a patient develops lymphoma while receiving TNF inhibitor therapy?

2.0 KEY KNOWN SAFETY RISKS OF TNF INHIBITOR THERAPY

1. How to manage patients with history of malignancy?

The risk of malignancies with TNF inhibitor therapy is discussed in detail in Section 2.2 of this document.

No adequate and well-controlled trials have evaluated the use of TNF inhibitors in patients with a history of any type of malignancy.

Analysis of data from the BSRBR, a registry in the UK, evaluating the influence of TNF inhibitor treatment on cancer incidence in RA patients with a history of malignancy, indicates that the incidence of malignancies in such patients was not increased compared to RA patients with prior malignancy treated with traditional DMARDs. (Dixon 2010)

The decision to use adalimumab in a patient with a history of malignancy should be made at the discretion of the physician based on a careful evaluation of the benefit and risk to the individual patient. Heightened monitoring and screening for the possible appearance of all malignancies during and after treatment with a TNF inhibitor is strongly recommended for all patients receiving adalimumab. Physicians should educate patients, their families and caregivers about the signs and symptoms of malignancies and urge them to notify their physician if any unusual signs or symptoms develop.

2. What do you do with a patient who requires a biologic who has had breast cancer in the last 5 years?

No adequate and well-controlled trials have evaluated the use of TNF inhibitors in patients with a history of any type of malignancy, including breast cancer.

AbbVie has not evaluated the risk of recurrence of malignancy during adalimumab treatment in patients with less than 5 years history of breast cancer or other malignancies.

In general, the potential risk of recurrent malignancies in patients receiving TNF inhibitor therapy, including adalimumab, has not been well studied. A report of the use of adalimumab in a patient with a history of breast carcinoma was described in the findings from a 20-week study (Pitarch 2006). This study evaluated the efficacy and safety of adalimumab given as monotherapy 40 mg every other week in 9 patients with Ps and PsA who were refractory to previous therapies, including other TNF inhibitors. Upon

completion of the 20-week study, patients were able to continue receiving TNF inhibitor therapy. This study included a 46-year-old woman with a history of infiltrating intraductal breast carcinoma, which was in complete remission at study baseline after being treated 20 months prior to the initiation of adalimumab. She had previously been treated with multiple systemic therapies, including cyclosporine, etretinate, MTX, psoralen, and ultraviolet A, alefacept, and infliximab. Following treatment with adalimumab for 1 year under close observation, she had no evidence of cancer relapse.

Data on the long-term history of patients with treated breast cancer is limited. One published report stated that there is no evidence to suggest that TNF inhibitor therapy cannot be initiated in patients with a history of previous malignancy if they have been recurrence-free for 10 years or more. (Ledingham 2005)

The decision to treat a patient with a history of malignancy with adalimumab should be made at the discretion of the physician based on a careful evaluation of the benefit and risk for the individual patient. Heightened monitoring and screening for the possible appearance of malignancies during and after treatment with TNF inhibitors is strongly recommended for all patients receiving adalimumab. UC patients are to be screened for dysplasia and colon cancer at regular intervals before therapy and throughout their disease course because of the increased risk of colon cancer regardless of therapy. This evaluation should include colonoscopies and biopsies as per local recommendations. Current evidence does not provide evidence whether or not adalimumab treatment influences the risk for developing dysplasia or colon cancer in UC patients.

3. Can you start a TNF inhibitor in a patient who is currently being treated for cancer (breast cancer/lung cancer/other)?

No studies have been conducted to address this question.

2.0 KEY KNOWN SAFETY RISKS OF TNF INHIBITOR THERAPY

4. Does TNF inhibitor therapy increase the risk of new cancers in patients with a prior history of malignancy?

No clinical trials have been conducted to address this question. Advice in the following guidances is provided below:

The second European consensus on the diagnosis and treatment of Crohn's disease published in 2010 enhanced the European Crohn's and Colitis Organisation (ECCO) guidelines recommending that for patients with a history of a non-hematopoietic cancer, careful consideration should be given whether or not to initiate TNF inhibitor therapy. (Dignass 2010) When in doubt, advice from an oncologist or specialist in infectious diseases should be sought.

A recent update to the British Society of Rheumatology (BSR) guidelines note that the effects of TNF inhibitor therapies are unknown in patients with a pre-existing malignancy or a lymphoproliferative disease. (Ledingham 2005)

The effect of TNF inhibitor therapies on pre-malignant conditions such as Barrett's esophagus, cervical dysplasia, and large bowel polyps is not known either. In general, caution should be exercised in the use of TNF inhibitor therapies in patients with previous malignancy or pre-malignant conditions. The potential benefits of treatment need to be considered against the risks related to potential recurrence/onset of the specific malignancy. However, for those patients with a history of previous malignancy but who have been free of recurrent disease for 10 years or more, there is no evidence for a contraindication to TNF inhibitor therapy.

The decision to use adalimumab in a patient with a history of malignancy should be made at the discretion of the physician based on a careful evaluation of the risk-benefit balance for the specific patient. Additional caution should be exercised in considering adalimumab treatment for these patients. Heightened monitoring and surveillance for the possible appearance of malignancies during and after treatment with TNF inhibitors is strongly recommended for all patients receiving adalimumab.

5. Does the use of TNF inhibitor therapy increase the risk of skin cancer?

There is an increased risk of NMSC among patients treated with TNF inhibitors. (Mariette 2011) During

the controlled portions of pivotal adalimumab trials at least 12 weeks in duration in patients with moderately

to severely active RA, PsA, AS, CD, UC, and Ps, the rate of NMSC was 9.7 per 1000 patient-years among adalimumab-treated patients and 5.1 per 1000 patient-years among control patients. Of these skin cancers, squamous cell carcinomas occurred at rates of 2.6 per 1000 patient-years among adalimumab-treated patients and 0.7 per 1000 patient-years among control patients.

All patients, and in particular patients with a medical history of extensive immunosuppressant therapy or psoriasis patients with a history of PUVA treatment, should be examined for the presence of NMSC prior to, and during, treatment with adalimumab.

6. Does the use of a biologic increase the risk of recurring lymphoma in patients who have a prior history of lymphoma?

No studies have been conducted that include patients with a history of lymphoma or other malignancies. There is, however, an increased risk of lymphoma in RA patients with long-standing, highly active, inflammatory disease prior to biologic therapy, which complicates the estimation of the risk.

According to the BSR, "The effects of [TNF inhibitor] therapies are as yet unknown in patients with pre-existing malignancy or lymphoproliferative disease. Caution should be exercised in the use of [TNF inhibitors] in patients with previous malignancy. The potential benefits of treatment need to be considered against the risks related to potential recurrence of the specific malignancy. If patients have been free of any recurrence of their malignancy for 10 years there is no evidence for a contraindication to [TNF inhibitor] therapy." (Ledingham 2005)

Given the lack of relevant data, caution should be exercised in considering adalimumab treatment for these patients. (Hudson 2010) The use of adalimumab in a patient with a history of malignancy is at the discretion of the healthcare professional based on a careful evaluation of the benefits and the risks in each individual patient. (Colombel 2009)

2.0 KEY KNOWN SAFETY RISKS OF TNF INHIBITOR THERAPY

7. What do you do if a patient develops lymphoma while receiving TNF inhibitor therapy?

No studies have been conducted evaluating management of patients who develop lymphoma or other malignancies while receiving adalimumab.

According to the BSR, “Patients should be investigated for potential malignancy if clinically suspected and consideration should be given to stopping [TNF inhibitor] treatment if malignancy is confirmed.” (Ledingham 2005)

2.3 Congestive Heart Failure

Adalimumab has not been formally studied in patients with congestive heart failure (CHF). However, in clinical studies with another TNF inhibitor, a higher rate of serious CHF-related adverse events, including worsening CHF and new onset CHF, have been reported.

Increased circulating levels of TNF have been identified in patients with CHF, primarily in patients with advanced chronic heart failure. (Levine 1990) Tumor necrosis factor has been associated with left ventricular dysfunction, cardiomyopathy, and pulmonary edema. (Coletta 2002) The observation that proinflammatory cytokines were capable of modulating left ventricular function prompted a series of clinical trials using targeted approaches to neutralize the effects of TNF in patients with moderate to advanced heart failure. (Mann 2002) The use of etanercept in the treatment of heart failure was evaluated in 2 large clinical trials which were terminated early due to lack of efficacy. (Enbrel® Package Insert 2013) Results of one of the trials suggested higher mortality in patients treated with etanercept compared to placebo. In a randomized study evaluating infliximab in moderate to severe heart failure, higher incidences of mortality and hospitalization due to worsening heart failure were observed in patients receiving 10 mg/kg infliximab doses compared with 5 mg/kg infliximab and placebo. (Remicade® Package Insert 2015) Trends toward increased dyspnea, hypotension, angina, and dizziness in both the 10 mg/kg and 5 mg/kg treatment groups were observed, versus placebo. Additionally, at 1 year, 8 patients in the 10 mg/kg infliximab group had died compared with 4 deaths each in the 5 mg/kg infliximab group and placebo group.

According to the 2012 American College of Rheumatology recommendations for the use of nonbiologic and biologic DMARDs in patients with RA, use of TNF inhibitor therapy is not recommended in patients with New York Heart Association (NYHA) class III or IV CHF and a left ventricular ejection fraction \leq 50%. (Singh 2012) The 2008 American Academy of Dermatology guidelines of care for the management of Ps and PsA recommend that patients with NYHA class III or IV CHF avoid the use of TNF inhibitor therapy and that patients with milder CHF have TNF inhibitor therapy discontinued with the onset of new symptoms or worsening of pre existing CHF. (Menter 2008) Additionally, patients with NYHA class I or II CHF should undergo echocardiogram testing and, if an ejection fraction $<$ 50% is identified, TNF inhibitor therapy should potentially be avoided.

Physicians should exercise caution when using adalimumab in patients who have heart failure and monitor them carefully.

In order to minimise the risk of congestive heart failure in patients treated with adalimumab:

- > Adalimumab must not be administered to patients with moderate to severe heart failure (NYHA class III/IV).
- > Adalimumab should be used with caution in patients with mild heart failure (NYHA class I/II).
- > Treatment with adalimumab must be discontinued in patients who develop new or worsening symptoms of congestive heart failure.

Cardiovascular Risk – Frequently Asked Questions

1. Does the use of biologics increase the risk of developing congestive heart failure (CHF)?

1. Does the use of biologics increase the risk of developing congestive heart failure (CHF)?

Cases of worsening CHF and new-onset CHF have been reported with TNF inhibitors). Cases of worsening CHF have also been observed with adalimumab. As a result, adalimumab should be used with caution in patients with heart failure (NYHA class I/II).

2.0 KEY KNOWN SAFETY RISKS OF TNF INHIBITOR THERAPY

The inclusion of increased CHF risk in the Humira label is largely based on findings from clinical studies evaluating etanercept and infliximab treatments. Results of a study evaluating the use of etanercept in the treatment of heart failure suggested higher mortality in patients treated with etanercept compared to placebo. (Enbrel® Package Insert 2013 In addition, a randomized study evaluating infliximab in moderate to severe heart failure, higher incidences of mortality and hospitalization due to worsening heart failure were observed in patients receiving 10 mg/kg infliximab doses compared with 5 mg/kg infliximab and placebo. (Remicade® Package Insert 2015 The results of 2 non-related studies also indicated an increased risk of CHF with TNF inhibitors. (Curtis 2007; Setoguchi 2008) However, several papers from registries have shown reductions, or no changes, in incident rates of CHF in subjects treated with TNF inhibitors compared to matched controls. (Wolfe 2004; Carmona 2007; Listing 2008; Cole 2007; Bernatsky 2005)

The conflicting findings of the aforementioned studies make it difficult to determine whether TNF inhibitor treatment increases the risk of CHF; consequently, physicians should take caution in monitoring for CHF during TNF inhibitor therapy, as appropriate.

Treatment with adalimumab should be discontinued in patients who develop new or worsening symptoms of CHF.

2.4 Demyelinating Diseases

TNF inhibitors, including adalimumab, have been associated in rare cases with new onset or worsening of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis and optic neuritis, and peripheral demyelinating disease, including Guillain Barré syndrome. ()

Tumor necrosis factor and its receptor system are important mediators of inflammation in RA. (Mori 1996) Multiple theories have been proposed to explain a potential biologic relationship between TNF and the demyelinating process. Theories include: 1) TNF inhibitors may disturb a latent infection that could incite an autoimmune demyelinating process, (Andersen 2008; Robinson 2001) 2) TNF inhibitors may disrupt the intrinsic balance of TNF and its receptors in the peripheral nervous system, (Shin 2006; Andersen 2008)

3) TNF has another function within the brain that has not been identified, (Andersen 2008) and 4) TNF inhibitors may induce a transformed gradient of TNF on each side of the blood-brain barrier causing an upregulation of TNF resulting in inflammation and demyelination.

A systematic review of the literature was conducted to identify the occurrence of demyelinating disease, particularly MS, occurring spontaneously or coincident with biologic therapy in patients with IBD. (Andersen 2008) Additionally, an assessment of a national Danish TNF inhibitor-treated IBD cohort was performed to identify and describe cases of demyelinating disease to compare the occurrence of MS in the TNF inhibitor cohort to the general Danish population. The occurrence of MS was calculated as a standardized morbidity ratio (SMR) defined by the observed number of cases in the Danish IBD TNF inhibitor cohort divided by the expected number in the general Danish population.

The systematic literature review identified up to a 4-fold risk of demyelinating disease, in particular MS, in patients with IBD independent of medical treatment. Four of the 651 patients in the Danish IBD TNF inhibitor cohort developed demyelinating disease, of which a confirmed diagnosis of MS was made in only 1 patient. The complete resolution of the demyelinating events in the other 3 patients following discontinuation of the TNF inhibitor suggests a causal link between treatment and the development of a neurological complication. The SMR was 4.2 in the Danish cohort, but the result did not reach statistical significance. The risk of developing MS in the TNF inhibitor treated patients did not exceed the risk of demyelinating disease, in particular MS, in IBD patients not treated with TNF inhibitors identified in the literature review.

There is a known association between demyelinating disorders and intermediate uveitis. (Zein 2004; Llorens 2012; Messenger 2015). Across all adalimumab clinical programs, the rate of demyelinating disorders was <0.1 events/ 100PYs (Investigator's Brochure Ed 21). For the uveitis clinical programs the rate was 0.9 events/100PYs (Investigator's Brochure Ed 21). An internal epidemiological study showed the rate of demyelinating disorders observed in the uveitis clinical program was of the same magnitude as the background rate expected in uveitis patients unexposed to adalimumab [Summary of Clinical Safety,

Integrated Summary of Safety, R &D/15/0263; AbbVie Epidemiology Report on file - Prevalence and Incidence of Demyelinating Diseases in Patients with Uveitis: a Health Insurance Claims-Based Study, August 31 2015]. This internal epidemiology study, consistent with published literature, also showed the highest incidence rate of demyelination/multiple sclerosis in the intermediate uveitis subtype (Llorens 2012). Overall, patients with intermediate uveitis are at an increased risk of developing demyelinating disorders independent of biologic therapy.

In order to minimise the risk of demyelinating disorders occurring in patients treated with adalimumab:

- Prescribers should exercise caution in considering the use of adalimumab in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders. Discontinuation of adalimumab should be considered if any disorders develop
- Due to the known association between intermediate uveitis and central demyelinating disorders, neurologic evaluation (i.e. *consultation with a physician with expertise in the diagnosis of neurological disorders, detailed neurological history and physical examination, laboratory evaluations and/or imaging studies*) should be performed in patients with non-infectious intermediate uveitis prior to initiation of adalimumab therapy and regularly during treatment to assess for pre-existing or developing central demyelinating disorders.

3.0 SAFETY ACROSS INDICATIONS

3.0 Safety Across Indications

The cumulative rates of serious adverse events were evaluated in a meta-analysis of 71 global clinical trials of adalimumab across 6 indications, involving 23,458 patients. (Burmester 2013) The rates per 100 PYs of serious adverse events of interest are provided in Table 1. The most frequently reported serious adverse events have been infections. The rate of serious

infections in the adalimumab RA trials was 4.6 events/100 PYs. The rate of serious infection in CD trials (6.7 events/100 PYs) was higher than in the other indications. Many of these events were intra-abdominal or other GI-related abscesses, which are common in the CD patient population in general.

TABLE 1 > SERIOUS ADVERSE EVENTS OF INTEREST WITH ADALIMUMAB BY APPROVED INDICATION

Finding	Burmester 2013					
	RA	PsA	AS	JIA	Ps	CD
N	14,109	837	1,684	212	3,010	3,606
Exposure (PYs)	23,942.6	997.5	1,985.6	604.9	5061.8	4,138.0
Events/100 PYs						
Serious infections	4.6	2.8	1.4	2.0	1.7	6.7
TB	0.3	0.2	0	0	0.1	< 0.1
Opportunistic infections	< 0.1	0	0	0	0	2.0
Malignancies (excluding lymphoma and NMSC)	0.9	0.2	0.2	0	0.6	0.5
Lymphoma	0.1	0.2	< 0.1	0	< 0.1	< 0.1
NMSC	0.2	0.1	0.3	0	0.1	< 0.1
Melanoma	< 0.1	0	< 0.1	0	0.2	0.1
Demyelinating disorders	< 0.1	0	< 0.1	0	0	0.1
Lupus-like syndrome	< 0.1	0	0.1	0	0	< 0.1
CHF	0.2	0	0.1	0	0	0
New onset/worsening psoriasis	< 0.1	0.1	< 0.1	0	< 0.1	< 0.1
Any adverse event leading to death	0.8	0.3	< 0.1	0	0.2	0.1

RA = rheumatoid arthritis; PsA = psoriatic arthritis; AS = ankylosing spondylitis; JIA = juvenile idiopathic arthritis; Ps = psoriasis; CD = Crohn's Disease.

Note: Rates are current as of 06 November 2010.

Source: Burmester 2013.

3.0 SAFETY ACROSS INDICATIONS

Other – Frequently Asked Questions

1. How does the duration of the biologic product's half-life affect its safety profile, in particular if a patient develops a serious infection?
2. What are the differences in safety among the various biologics?

1. How does the duration of the biologic product's half-life affect its safety profile, in particular if a patient develops a serious infection?

The time required for adalimumab concentrations to decrease by 50%, commonly referred to as the "half-life" of the product in the serum, has been determined to be approximately 4.5, 7 to 9, and 12 to 14 days for etanercept, infliximab, and adalimumab, respectively. Three to 5 half-lives are required for a drug to be completely eliminated from the body. There is no evidence that the duration of a biologic product's half-life is predictive of its safety profile, in particular the risk of developing serious infection.

If a serious infection occurs concurrently with the use of a biologic, the most important factor, consistent with the generally accepted approach to proper clinical management of serious infection, is to provide optimal treatment to control the infection and to discontinue biologic use. Because most bacterial infections respond to appropriate antibiotics in 1 to 3 days, the half-life of a biologic is not a critical factor with regard to providing effective treatment of serious bacterial infection.

Below are some relevant key facts in regard to serious infection in the context of biologic use:

- > Once a serious infection is recognized the critical time to treatment with appropriate antibiotic therapy is 24 hours
- > Based on the treatment window for most bacterial infections, the half-lives of adalimumab and etanercept are such that both agents would not be expected to be cleared from the body before the infection is resolved, either through their natural course or through antibiotics
- > Differences in half-life between agents can be expected to be relevant only in terms of the time needed for clearance after a drug is discontinued
- > The half-lives of all 5 TNF inhibitors exceed the time frame of most infectious medical urgencies

- > Most bacterial infections respond to appropriate antibiotics in 1 to 3 days, i.e., sooner than the half-life of any TNF inhibitor
- > Administration of adalimumab should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until infections are controlled

2. What are the differences in safety among the various biologics?

No head-to-head trials have been conducted comparing the safety profiles of the various marketed biologics, and therefore, the differences, if any exist, cannot be accurately described.

4.0 GLOSSARY OF TERMS

AAD	American Academy of Dermatology	PML	Progressive multifocal leukoencephalopathy
ACR	American College of Rheumatology	PPD	Purified protein derivative
AGA	American Gastroenterological Association	PYs	patient-years
ALT	Alanine transaminase	Ps	Psoriasis
ANA	antinuclear antibody	PsA	Psoriatic arthritis
anti-dsDNA	anti double stranded DNA	RA	Rheumatoid arthritis
AS	Ankylosing spondylitis	SAE	Serious adverse event
CD	Crohn's disease	SC	subcutaneous
AUC	Area under the curve	SCC	Squamous cell carcinoma
BCC	Basal cell carcinoma	SIR	Standardized incidence ratio
BCG	Bacille Calmette-Guérin	TB	Tuberculosis
BSR	British Society of Rheumatology	TNF	Tumor necrosis factor
BSRBR	British Society for Rheumatology Biologics Registry	UC	Ulcerative colitis
CD	Crohn's disease	US	United States
CHF	Congestive heart failure	WHO	World Health Organization
CI	Confidence interval		
CNS	Central nervous system		
CSF	Cerebrospinal fluid		
DMARD	Disease-modifying antirheumatic drug		
ECCO	European Crohn's and Colitis Organisation		
EMA	European Medicines Agency		
eow	every other week		
GI	Gastrointestinal		
HBV	Hepatitis B virus		
HCP	Healthcare practitioner		
HL	Hodgkin's lymphoma		
HSTCL	Hepatosplenic T-cell lymphoma		
IBD	Inflammatory bowel disease		
IgG1	Immunoglobulin		
JIA	Juvenile idiopathic arthritis		
MS	Multiple sclerosis		
MTX	Methotrexate		
NCI	National Cancer Institute		
NHL	Non-Hodgkin's lymphoma		
NMSC	Non-melanoma skin cancer		
nr-axSpA	non-radiographic axial spondyloarthritis		
NYHA	New York Heart Association		
OTIS	Organization of Teratology and Information Services		
PK	pharmacokinetic		

5.0 REFERENCES

- Ampel NM. Coccidioidomycosis. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson LJ, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 17th ed. New York, NY: McGraw-Hill Companies, Inc; 2008:chap 193.
- Andersen NN, Caspersen S, Jess T, et al. Occurrence of demyelinating diseases atier anti TNF α treatment of inflammatory bowel disease: a Danish Crohn Colitis Database study. *J Crohns Colitis*. 2008;2(4):304-309.
- Belhadj K, Reyes F, Farcet JP, et al. Hepatosplenic $\gamma\delta$ T-cell lymphoma is a rare clinicopathologic entity with poor outcome: report on a series of 21 patients. *Blood*. 2003;102(13):4261-4269.
- Bergstrom L, Yocum DE, Ampel NM, et al. Increased risk of coccidioidomycosis in patients treated with tumor necrosis factor alpha antagonists. *Arthritis Rheum*. 2004;50:1959-1966.
- Bernatsky S, Hudson M, Suissa S. Anti-rheumatic drug use and risk of hospitalization for congestive heart failure in rheumatoid arthritis. *Rheumatol*. 2005;44(5):677-680.
- Bernheim O, Scherl E, Bosworth B. Hepatosplenic T-cell lymphoma atier sequential infliximab, adalimumab and natalizumab therapy for Crohn's disease [abstract]. *Am J Gastroenterol*. 2009;104(suppl 3):S359. Abstract 977.
- Brown TER, Chin TWF. Superficial fungal infections. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 7th ed. New York, NY: McGraw-Hill Companies, Inc; 2008: chap 124.
- Bruns H, Meinken C, Schauenberg P, et al. Anti-TNF immunotherapy reduces CD8+ T-cell-mediated antimicrobial activity against *Mycobacterium tuberculosis* in humans. *J Clin Invest*. 2009;119(5):1167-1177.
- Burmester GR, Panaccione R, Gordon KB, et al. Adalimumab: long-term safety in 23,458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. *Ann Rheum Dis*. 2013;72:517-524.
- Carmona L, Descalzo MA, Perez-Pampin E, et al. All-cause and cause-specific mortality in rheumatoid arthritis are not greater than expected when treated with tumour necrosis factor antagonists. *Ann Rheum Dis*. 2007;66(7):880-885.
- Carver PL. Invasive fungal infections. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 7th ed. New York, NY: McGraw-Hill Companies, Inc; 2008: chap 125.
- Chapman SW, Sullivan DC. Blastomycosis. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson LJ, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 17th ed. New York, NY: McGraw-Hill Companies, Inc; 2008: chap 194.
- Cole J, Busti A, Kazi S. The incidence of new onset congestive heart failure and heart failure exacerbation in Veteran's Affairs patients receiving tumor necrosis factor alpha antagonists. *Rheumatol Int*. 2007;27(4):369-373.
- Coletia AP, Clark AL, Banarjee P, et al. Clinical trials update: RENEWAL (RENAISSANCE and RECOVER) and ATTACH. *Eur J Heart Fail*. 2002;4(4):559-561.
- Colombel JF, Sandborn WJ, Panaccione R, et al. Adalimumab safety in global clinical trials of patients with Crohn's disease. *Inflamm Bowel Dis*. 2009;15:1308-1319.
- Cooke CB, Krenacs L, Stetler-Stevenson M, et al. Hepatosplenic T-cell lymphoma: a distinct clinicopathologic entity of cytotoxic $\gamma\delta$ T-cell origin. *Blood*. 1996;88(11):4265-4274.
- Curtis JR, Kramer JM, Martin C, et al. Heart failure among younger rheumatoid arthritis and Crohn's patients exposed to TNF-alpha antagonists. *Rheumatol*. (Oxford). 2007;46(11):1688-1693.
- Dignass A, Van Assche G, Lindsay JO, et al. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: current management. *J Crohns Colitis*. 2010;4(1):28-62.
- Dinh V, et al. Merkel cell carcinomas. *Hematol Oncol Clin North Am*. 2007;21(3):527-544.
- Dixon WG, Watson KD, Lunt M, et al. Influence of anti-tumor necrosis factor therapy on cancer incidence in patients with rheumatoid arthritis who have had a prior malignancy: results from the British Society for Rheumatology Biologics Register. *Arthritis Care and Research*. 2010;62(6):755-763.
- Doherty SD, Van Voorhees A, Lebwohl MG, et al. National Psoriasis Foundation consensus statement on screening for latent tuberculosis infection in patients with psoriasis treated with systemic and biologics agents. *J Am Acad Dermatol*. 2008;59(2):2009-2217.
- Enbrel® [package insert]. Thousand Oaks, CA: Immunex Corporation; 2013.
- Flynn JL, Goldstein MM, Chan J, et al. Tumor necrosis factor- α is required in the protective immune response against *Mycobacterium tuberculosis* in mice. *Immunity*. 1995;2(6):561-572.
- Furst DE, Schiff MH, Fleischmann RM, et al. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). *J Rheumatol*. 2003;30(12):2563-71.
- Galloway JB, Hyrich KL, Mercer LK, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. *Rheumatology (Oxford)*. 2011;50(1):124-31. Epub 2010 Jul 31.
- Greenberg JD, Reed G, Kremer JM, et al. Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. *Ann Rheum Dis*. 2010;69(2):380-386.
- Harris J, Hope JC, Keane J. Tumor necrosis factor blockers influence macrophage responses to *Mycobacterium tuberculosis*. *J Infect Dis*. 2008;198(12):1842-1850.
- Herbein G, O'Brien WA. Tumor necrosis factor (TNF) α and TNF receptors in viral pathogenesis. *Proc Soc Exp Biol Med*. 2000;223(3):241-257.
- Hudson M, Suissa S. Avoiding common pitfalls in the analysis of observational studies of new treatments for rheumatoid arthritis. *Arthritis Care Res*. 2010;62(6):805-810.
- Humira Company Core Data Sheet. North Chicago, IL: AbbVie, 2013.
- Kasahara S, Ando K, Saito K, et al. Lack of tumor necrosis factor alpha induces impaired proliferation of hepatitis B virus specific cytotoxic T lymphocytes. *J Virol*. 2003;77(4):2469-2476.
- Khan WA, Yu L, Eisenbrey AB, et al. Hepatosplenic gamma/delta T-cell lymphoma in immunocompromised patients: report of two cases and review of literature. *Am J Clin Pathol*. 2001;116(1):41-50.
- Kraus MD, Crawford DF, Kaleem Z, et al. T $\gamma\delta$ hepatosplenic lymphoma in a heart transplant patient atier an Epstein-Barr virus positive lymphoproliferative disorder: a case report. *Cancer*. 1998;82(5):983-992.
- Ledingham J, Deighton C. Update on the British Society for Rheumatology guidelines for prescribing TNF alpha blockers in adults with rheumatoid arthritis (update of previous guidelines of April 2001). *Rheumatology (Oxford)*. 2005;44(2):157-163.
- Lee J-H, Slifman NR, Gershon SK, et al. Life-threatening histoplasmosis complicating immunotherapy with tumor necrosis factor α antagonists infliximab and etanercept. *Arthritis Rheum*. 2002;46(10):2565-2570.
- Levine B, Kalman J, Mayer L, et al. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. *N Engl J Med*. 1990;323(4):236-241.
- Lichtenstein GR, Hanauer SB, Sandborn WJ. Management of Crohn's Disease in Adults. *AM J Gastroenterol*. 2009;104:465-483.
- Listing J, Strangfeld A, Kewok J, et al. Does tumor necrosis factor alpha inhibition promote or prevent heart failure in patients with rheumatoid arthritis? *Arthritis Rheum*. 2008;58(3):667-677.
- Llorens V, Rey A, Mesquida M, et al. Central nervous system demyelinating disease-associated uveitis. *Arch Soc Esp Ophthalmol*. 2012;87(10):324-9.
- Lorber B. *Listeria monocytogenes*. In: Mandell GL, Bennett JB, and Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 7th ed. Philadelphia, PA: Churchill Livingstone, an Imprint of Elsevier; 2009: chap 207.
- Mackey AC, Green L, Liang L, et al. Hepatosplenic T-cell lymphoma associated with infliximab use in young patients treated for inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2007;44(2):265-267.
- Mackey AC, Green L, Leptak C, et al. Hepatosplenic T-cell lymphoma associated with infliximab use in young patients treated for inflammatory bowel disease: update [letter]. *J Pediatr Gastroenterol Nutr*. 2009;48(3):386-388.
- Marietie X, Matucci-Cerinic M, Pavelka K, et al. Malignancies associated with tumour necrosis factor inhibitors in registries and prospective observational studies: a systematic review and meta-analysis. *Ann Rheum Dis*. 2011;70(11):1895-1904.
- Mann DL. Inflammatory mediators and the failing heart: past, present, and the foreseeable future. *Circ Res*. 2002;91(11):988-998.
- Menter A, Gotlib A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. *J Am Acad Dermatol*. 2008;58(5):826-850.
- Messenger W, Hildebrandt L, Mackensen F et al. Characterisation of uveitis in association with multiple sclerosis. *Br J Ophthalmol*. 2015;99:205-209
- Mori L, Iselin S, De Libero G, et al. Attenuation of collagen induced arthritis in 55 kDa TNF receptor type 1 (TNFR1) IgG1 treated and TNFR1 deficient mice. *J Immunol*. 1996;157(7):3178-3182.
- Nathan DM, Angus PW, Gibson PR. Hepatitis B and C virus infections and anti tumor necrosis factor α therapy: guidelines for clinical approach. *J Gastroenterol Hepatol*. 2006;21(9):1366-1371.
- Navarro JT, Ribera JM, Mate JL, et al. Hepatosplenic T-gammadelta lymphoma in a patient with Crohn's disease treated with azathioprine. *Leuk Lymphoma*. 2003;44(3):531-533.
- Perez J, Kupper H, Spencer-Green G. Impact of screening for latent TB before initiating anti-TNF therapy in North America and Europe. *Ann Rheum Dis*. 2005;64(Suppl. 3):265.
- Pitarch G, Sanchez-Carazo JL, Mahiques L, et al. Treatment of psoriasis with adalimumab. *Clin Exp Dermatol*. Remicade® [package insert]. Horsham, PA: Centocor Ortho Biotech, Inc; 2015.
- Robinson WH, Genovese MC, Moreland LW. Demyelinating and neurologic events reported in association with tumor necrosis factor α antagonism: by what mechanisms could tumor necrosis factor α antagonists improve rheumatoid arthritis but exacerbate multiple sclerosis? *Arthritis Rheum*. 2001;44(9):1977-1983.
- Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum*. 2008;59(6):762-784.
- Sabria M, Yu VL. Legionella infection. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson LJ, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 17th ed. New York, NY: McGraw-Hill Companies, Inc; 2008: chap 141.

5.0 REFERENCES

- Setoguchi S, Schneeweiss S, Avorn J, et al. Tumor necrosis factor-alpha antagonist use and heart failure in elderly patients with rheumatoid arthritis. *Am Heart J*. 2008;156(2):336-341.
- Shin I SJ, Baer AN, Kwon HJ, et al. Guillain Barré and Miller Fisher syndromes occurring with tumor necrosis factor α antagonist therapy. *Arthritis Rheum*. 2006;54(5):1429-1434.
- Sieper J, Rudwaleit M, Baraliakos X, et al. The Assessment of Spondyloarthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis*. 2009;68(suppl 2):ii1-ii44.
- Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2012;64(5):625-639.
- Smitien AL, Choi HK, Hochberg MC, et al. The risk of hospitalized infection in patients with rheumatoid arthritis. *J Rheumatol*. 2008;35:387-393.
- Thayu M, Markowitz JE, Mamula P, et al. Hepatosplenic T-cell lymphoma in an adolescent patient atier immunomodulator and biologic therapy for Crohn disease. *J Pediatr Gastroenterol Nutr*. 2005;40(2):220-222.
- Walzer PD, Smulian AG. Pneumocystis species. In: Mandell GL, Benneti JB, and Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 7th ed. Philadelphia, PA: Churchill Livingstone, an Imprint of Elsevier; 2009: chap 270.
- Weidmann E. Hepatosplenic T-cell lymphoma. A review on 45 cases since the first report describing the disease as a distinct lymphoma entity in 1990. *Leukemia*. 2000;14(6):991-997.
- Wolfe F, Michaud K. Heart failure in rheumatoid arthritis: rates, predictors, and the effect of anti-tumor necrosis factor therapy. *Am J Med*. 2004;116(5):305-311.
- Zeidan A, Sham R, Shapiro J, et al. Hepatosplenic T-cell lymphoma in a patient with Crohn's disease who received infliximab therapy [letter]. *Leuk Lymphoma*. 2007;48(7):1410-1413.
- Zein G, Berta A, Foster CS. Multiple sclerosis associated uveitis. *Ocul Immunol Inflamm*. 2004;12(2):137-42.

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Datum izrade materijala: Prosinac, 2016.

Humira 40 mg otopina za injekciju (adalimumab). Lijek se izdaje na recept.

Sastavni dio ovog materijala za Humiru predstavlja i cjelokupan odobreni Sažetak opisa svojstava lijeka.

Prije propisivanja lijeka Humira, molimo pročitajte odobreni Sažetak opisa svojstava lijeka/uputu o lijeku, uključujući detaljne informacije o indikacijama, kontraindikacijama, nuspojavama, mjerama opreza te doziranju i načinu primjene.

Samo za zdravstvene radnike.

Nositelj odobrenja za stavljanje lijeka u promet: AbbVie Ltd, Maidenhead, Ujedinjeno Kraljevstvo.

Predstavnik nositelja odobrenja: Abbvie d.o.o., Strojarska 20, 10 000 Zagreb, tel: 01 5625 501, fax: 01 5625 560.

Brojevi odobrenja za stavljanje lijeka u promet: EU/1/03/256/001-019

ADCRHUM160473