SAFETY MONOGRAPH

This booklet contains important safety information about Humira® (adalimumab) and advice on risk minimisation.

This booklet was developed by AbbVie

Date of approval: February 2017

HUMIRA
adalimumab

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Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the Medicines Authority at: http://www.medicinesauthority.gov.mt/adrportal and to AbbVie Ltd via the local representative of AbbVie Ltd.: V.J. Salomone Pharma Ltd., Upper Cross Road, Marsa MRS1542, Malta, Tel: +356 21 220 174; or directly to AbbVie at ukadverseevents@abbvie.com

In order to support effective tracking and traceability of all biologics including biosimilars, it is recommended that the brand name and batch number are recorded

1.0 Introduction

Tumour necrosis factor (TNF) antagonists have offered significant benefits to many patients. There are some risks associated with these treatments, hence effective communication is essential for patient safety and management. This safety monograph is one component of an adalimumab safety educational program AbbVie has initiated for healthcare professionals. The purpose of this safety monograph is three-fold:

1. To inform physicians and other healthcare professionals about the key risks associated with the use of TNF antagonists such as adalimumab (HUMIRA®).

2. To help healthcare professionals in screening and monitoring patients appropriately while they are receiving TNF antagonist therapy.

3. To provide a tool for healthcare professionals in counselling patients about the risks of TNF antagonist therapy and the importance of timely reporting of any relevant signs or symptoms.

Adalimumab has a well-established safety profile across multiple indications based on more than 15 years of clinical trial experience and over 8 years of postmarketing experience. Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences. Adalimumab was created using phage display technology resulting in fully human heavy and light chain variable regions, which confer specificity to human TNF, and human IgG1 heavy chain and kappa light chain sequences. Adalimumab binds with high affinity and specificity to soluble tumour necrosis factor (TNF-α) but not lymphotoxin (TNF-β). Adalimumab is produced by recombinant DNA technology in a mammalian cell expression system. It consists of 1,330 amino acids and has a molecular weight of approximately 148 kilodaltons.

2.0 Key Safety Risks of TNF Antagonist Therapy

2.1 Serious Infections

Patients taking TNF-antagonists are more susceptible to serious infections, including diverticulitis and opportunistic infections (e.g. tuberculosis, invasive fungal infections, parasitic infections and legionellosis). These infections have not consistently been recognised in patients taking TNF-antagonists and this resulted in delays in appropriate treatment, sometimes resulting in fatal outcomes.

In the pivotal controlled trials in adults and children, the incidence of serious infections was 0.04 per patient year in adalimumab-treated patients and 0.03 per patient year in placebo and active control-treated patients.

In controlled and open-label adult and paediatric studies with adalimumab, serious infections (including fatal infections, which occurred rarely) including tuberculosis (both pulmonary and extra-pulmonary, i.e. disseminated) and invasive opportunistic infections (e.g. disseminated or extrapulmonary histoplasmosis, blastomycosis, coccidioidomycosis, pneumocystis, candidiasis, aspergillosis and listeriosis) were reported. Most of the cases of tuberculosis occurred within the first 8 months after initiation of therapy and may reflect recrudescence of latent disease. Other serious infections seen in clinical trials include pneumonia, pyelonephritis, septic arthritis and septicaemia.

The frequency of serious infections among adalimumab-treated subjects over 65 years of age (3.5%) was higher than for those under 65 years of age (1.45%). Some had fatal outcomes.

In order to minimise the risk of serious infections, prior to treatment with adalimumab:

- Physicians should exercise caution when considering the use of adalimumab in patients with a history of recurring infection or with underlying conditions which may predispose patients to infections, including the use of concomitant immunosuppressive medications. Particular attention regarding the risk for infection should be paid when treating the elderly, who are at increased risk. Impaired lung function may also increase the risk of serious infections.

- Treatment with adalimumab should not be initiated in patients with active infections, including chronic or localised infections, until infections are controlled.

- Adalimumab must not be initiated in patients who have severe infections, such as sepsis and opportunistic infections.

- All patients must be evaluated for evidence of active or inactive ("latent") tuberculosis infection prior to treatment with adalimumab. This evaluation should include a detailed medical assessment of patient history of tuberculosis or possible previous exposure to people with active tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests (e.g. tuberculin skin test, interferon gamma test, and chest x-ray) should be performed in all patients (local recommendations may apply). It is recommended that the conduct and results of these tests are recorded in the Patient Alert Card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

- If active tuberculosis is diagnosed, adalimumab therapy must not be initiated.

In order to minimise the risk of serious infections, prior to treatment with adalimumab:

- If latent tuberculosis is suspected, a physician with expertise in the treatment of tuberculosis should be consulted.

- If latent tuberculosis is diagnosed, appropriate treatment must be started with anti-tuberculosis prophylaxis treatment before the initiation of adalimumab, and in accordance with local recommendations.

- Use of anti-tuberculosis prophylaxis treatment should also be considered before the initiation of adalimumab in patients with several or significant risk factors for tuberculosis despite a negative test for tuberculosis and in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.

- In patients who have been exposed to tuberculosis and patients who have travelled in areas of high risk of tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis, the risk and benefits of treatment with adalimumab should be considered prior to initiating therapy.

- It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating adalimumab therapy.

- Administration of live vaccines to infants exposed to adalimumab in utero is not recommended for five months following the mother's last adalimumab injection during pregnancy.

In order to minimise the risk of serious infections, during treatment with adalimumab:

- Patients must be monitored closely for infections, including tuberculosis (before), during and after treatment with adalimumab. The elimination of adalimumab may take up to four months, therefore monitoring should be continued throughout this period. Some patients who have been successfully treated for active tuberculosis have redeveloped tuberculosis while being treated with adalimumab.

- 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 during or after therapy with adalimumab.

- Patients who develop a new infection while undergoing treatment with adalimumab, should be monitored closely and undergo a complete diagnostic evaluation.

- There may be a need for dose interruption, for instance before surgery or if a serious infection occurs.

- 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 the 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, an invasive fungal infection should be suspected and administration of adalimumab should be promptly discontinued. 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.

- Patients on adalimumab may receive concurrent vaccinations, except for live vaccines.

2.2 Malignancies

Malignancies, including lymphoma, non-melanoma skin cancer, melanoma, leukaemia, hepatosplenic T-cell lymphoma, and Merkel cell carcinoma, have been reported in patients receiving treatment with TNF-antagonists.

In the controlled portions of clinical trials of TNF-antagonists, more cases of malignancies, including lymphoma, were observed among patients receiving a TNF-antagonist compared with control patients. In the post-marketing setting, cases of leukaemia have been reported in patients treated with a TNF-antagonist.

There is an increased background risk for lymphoma and leukaemia in rheumatoid arthritis patients with long-standing, highly active inflammatory disease, which complicates the risk estimation.

Malignancies, including fatal cases, have been reported in children, adolescents and young adults treated with TNF-antagonists, including adalimumab. Approximately half these cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression.

Rare post-marketing cases of hepatosplenic T-cell lymphoma have been identified in patients treated with adalimumab. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Some of these hepatosplenic T-cell lymphomas with adalimumab have occurred in young adult patients on concomitant treatment with azathioprine or 6-mercaptopurine used for inflammatory bowel disease.

In an exploratory clinical trial evaluating the use of another TNF-antagonist, infliximab, in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, mostly in the lung or head and neck, were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking.

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

- All patients, and in particular patients with a medical history of extensive immunosuppressant therapy or psoriasis 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.

- It should be taken into careful consideration that there is potentially an increased risk of hepatosplenic T-cell lymphoma with combined treatments of azathioprine or 6-mercaptopurine and adalimumab.

- Caution should be exercised when using any TNF-antagonist in COPD patients, as well as in patients with increased risk for malignancy due to heavy smoking.

- Additional caution should be exercised in considering adalimumab in the treatment of patients that have a history of malignancy or in whom treatment with adalimumab is continued following development of malignancy.

- All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with longstanding ulcerative colitis or primary sclerosing cholangitis), or who had a history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations. With current data it is not known if adalimumab treatment influences the risk for developing dysplasia or colon cancer.

2.3 Demyelinating Disorders

TNF-antagonists have been associated in rare instances with new onset or exacerbation 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.

There is a known association between demyelinating disorders and intermediate uveitis. Across all adalimumab clinical programs, the rate of demyelinating disorders was <0.1 events/ 100PYs. For the uveitis clinical programs the rate was 0.9 events/100PYs.

An internal epidemiological study showed the rate of demyelinating disorders observed in the uveitis clinical program was not higher than the background rate expected in uveitis patients unexposed to adalimumab. This internal epidemiology study, consistent with published literature, also showed the highest incidence rate of demyelination/multiple sclerosis in the intermediate uveitis subtype. 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.

2.4 Congestive Heart Failure

In a clinical trial with another TNF-antagonist, worsening congestive heart failure and increased mortality due to congestive heart failure were observed. Cases of worsening congestive heart failure have also been reported in patients receiving adalimumab.

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.