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DEPARTMENT OF VETERANS AFFAIRS - VETERANS HEALTH ADMINISTRATION (VHA)
PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP), AND
CENTER FOR MEDICATION SAFETY PSCI (VA MEDSAFE)

CIMZIA (CERTOLIZUMAB PEGOL); ENBREL (ETANERCEPT); HUMIRA (ADALIMUMAB); REMICADE (INFLIXIMAB) AND THE RISK FOR INVASIVE FUNGAL INFECTIONS

I. ISSUE

The Food and Drug Administration (FDA) has required the manufacturers of the tumor necrosis factor- α (TNF) inhibitors to emphasize information about the risk of invasive fungal infections, such as histoplasmosis, in the *Warnings sections* of the product labeling and to add this safety issue as a *Boxed Warning* as well.

II. BACKGROUND

TNF antagonists act to suppress the immune-inflammatory cascade by inhibiting TNF- α , a proinflammatory cytokine which regulates inflammatory response. This action can facilitate immune-system related diseases. Due to this mechanism of action, all marketed TNF inhibitors currently include information about the risk of serious opportunistic infections in the *Boxed Warning* and *Warnings* sections of their respective product labeling. However the FDA has received case reports where inconsistent recognition and diagnosis of histoplasmosis and other invasive fungal infections have lead to treatment delays and fatalities in some instances.

Other complications observed with the use of these agents have included bacterial sepsis, tuberculosis, infections by mycobacteria other than tuberculosis (MOTT), and other opportunistic infections. The signs and symptoms of invasive fungal infection tuberculosis and infections by mycobacteria other than tuberculosis (MOTT) are often indistinguishable. Thus, patients with suspected signs and symptoms of invasive fungal infection should also be evaluated for infections by mycobacteria other than tuberculosis (MOTT).

III. DISCUSSION

Out of 240 reports of histoplasmosis in patients receiving TNF antagonists reviewed by the FDA, approximately 21 cases initially went unrecognized resulting in a delay of antifungal treatment. From these 21 patients, 12 died. In addition, FDA has received case reports of coccidioidomycosis and blastomycosis in patients receiving TNF antagonists. Death occurred in some of these cases.

Within the VA system, 1 case of disseminated fungal infection (histoplasmosis) associated with TNF inhibitor use was reported to the VA Adverse Drug Event Reporting System (VA ADERS) during March 1, 2007 – July 17, 2008.

IV. VA MEDSAFE RECOMMENDATIONS reinforce those of the FDA and include:

- Providers should closely monitor patients for the development of signs and symptoms of new infection during and after treatment with TNF inhibitors. Symptoms may include fever, malaise, weight loss, sweats, cough, dyspnea, pulmonary infiltrates, or serious febrile systemic illness including shock.
- Providers should discontinue TNF inhibitors in patients who develop a serious infection and perform a complete diagnostic workup (i.e., cultures for fungi and/or mycobacteria other than tuberculosis [MOTT], histopathological or cytological evaluations, antigen detection and serum antibody titers).
- Providers should consider systemic fungal infection processes or infections by mycobacteria other than tuberculosis (MOTT) in patients who develop a serious febrile or systemic illness if they reside or travel in endemic regions of mycoses.
- Providers should consult with an infectious diseases specialist, when appropriate, for decisions regarding empiric antimicrobial therapy in these patients.
- Providers may restart TNF inhibitor therapy after a patient has fully recovered from a serious infection and a reevaluation of the benefits and risks of TNF inhibitors (especially in patients who live in endemic areas), has been performed.
- Providers should document/report all possible adverse events related to TNF inhibitors, including serious ADEs, such as serious fungal and other infections, as per the usual protocols used at their VA (i.e., VHA's Adverse Drug Event Reporting Program and/or FDA's MedWatch program).
- Further information can be accessed via the following link: <http://www.fda.gov/bbs/topics/NEWS/2008/NEW01879.html>.

V. REFERENCES

1. Food and Drug Administration (FDA) Alert. 09/04/2008. <http://www.fda.gov/bbs/topics/NEWS/2008/NEW01879.html> .