

Health Canada Endorsed Important Safety Information on  
ENBREL<sup>®</sup> (etanercept)



Date April 21, 2009

Dear Health Care Professional:

**Subject: Risk of Histoplasmosis and Other Invasive Fungal Infections Associated with ENBREL<sup>®</sup> (etanercept)**

Amgen Canada, on behalf of Immunex, in collaboration with Health Canada, would like to inform you of updated safety information regarding ENBREL<sup>®</sup> (etanercept).

ENBREL<sup>®</sup> is a soluble form of a fully human tumour necrosis factor (TNF) receptor currently authorized in Canada for the treatment of rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis and plaque psoriasis. It is estimated that over 500,000 patients have been administered ENBREL<sup>®</sup> worldwide.

Amgen Canada has recently revised the **BOXED WARNING** and **WARNINGS AND PRECAUTIONS (Infections)** sections of the ENBREL<sup>®</sup> Product Monograph to clarify information regarding the risk of invasive fungal infections, including histoplasmosis, in patients taking ENBREL<sup>®</sup>. This change in the ENBREL<sup>®</sup> Product Monograph has been done primarily to increase awareness of the need for timely recognition and treatment of these infections.

- **There have been reports of serious pulmonary and disseminated histoplasmosis, coccidioidomycosis, blastomycosis infections, sometimes with fatal outcomes, in patients taking tumour necrosis factor- $\alpha$  blockers (TNF blockers), including Enbrel (etanercept).**
- **Histoplasmosis and other invasive fungal infections have not been recognized consistently in patients taking TNF blockers. This has led to delays in instituting appropriate treatment, sometimes resulting in death.**
- **For a patient taking a TNF blocker who presents with signs and symptoms of systemic illness, such as fever, malaise, weight loss, sweats, cough, dyspnea, and/or pulmonary infiltrates, the healthcare professional should ascertain if the patient has lived or worked in or traveled to areas of endemic mycoses. If so, appropriate empiric antifungal treatment may be initiated while a diagnostic workup is being performed. As with any serious infection, the TNF blocker should be stopped until the infection has been diagnosed and adequately treated.**

Although no histoplasmosis infections were reported among 17,696 patients from the United States and Canada who were treated with ENBREL® in 38 clinical trials and four cohort studies involving all authorized indications, post marketing cases of serious and sometimes fatal fungal infections, including histoplasmosis, have been reported with TNF blockers, including ENBREL®.

For patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if these patients develop a serious systemic illness. Appropriate empiric antifungal therapy may be initiated while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections.

A TNF blocker may be restarted after recovery from the infection. The decision to restart a TNF blocker should include a re-evaluation of the benefits and risks of the TNF blocker. Both the decision to restart TNF blocker therapy and the duration of antifungal therapy should be made in consultation with an infectious disease specialist, when feasible.

Prescribers should discuss with patients and their caregivers the risk for infections while receiving TNF blockers, including infections caused by viruses, fungi, or bacteria including tuberculosis (TB). Patients should be encouraged to promptly seek medical attention for symptoms such as weight loss, persistent fever, sweating, cough, shortness of breath, or fatigue.

The Canadian Product Monograph (CPM) has been revised to include information regarding the risk of invasive fungal infection. The CPM can be found at the following link:  
<http://www.amgen.ca/english/patients/products.html>.

Managing marketed health product-related adverse reactions depends on health care professionals and consumers reporting them. Reporting rates determined on the basis of spontaneously reported post-marketing adverse reactions are generally presumed to underestimate the risks associated with health product treatments. Any case of invasive fungal infection or other serious or unexpected adverse reaction in patients receiving ENBREL should be reported to Amgen Canada or Health Canada at the following addresses:

Amgen Canada Inc. on behalf of Immunex Corporation  
6775 Financial Drive, Suite 100  
Mississauga, Ontario L5N 0A4  
Tel: (866) 512-6436; Fax: (888) 264-3655  
[safetycanada@amgen.com](mailto:safetycanada@amgen.com)

**Any suspected adverse reaction can also be reported to:**

Canada Vigilance Program  
Marketed Health Products Directorate  
HEALTH CANADA  
Address Locator: 0701C  
Ottawa, Ontario, K1A 0K9  
Tel: 613-957-0337 or Fax: 613-957-0335  
To report an Adverse Reaction, consumers and health professionals may call toll free:  
Tel: 866-234-2345; Fax: 866-678-6789  
[CanadaVigilance@hc-sc.gc.ca](mailto:CanadaVigilance@hc-sc.gc.ca)

The [AR Reporting Form](#) and the [AR Guidelines](#) can be found on the Health Canada web site or in *The Canadian Compendium of Pharmaceuticals and Specialties*.

[http://hc-sc.gc.ca/dhp-mps/medeff/report-declaration/ar-ei\\_form-eng.php](http://hc-sc.gc.ca/dhp-mps/medeff/report-declaration/ar-ei_form-eng.php)

[http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/guide/2008-ar-ei\\_guide-ldir/index-eng.php](http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/guide/2008-ar-ei_guide-ldir/index-eng.php)

**For other inquiries related to this communication, please contact Health Canada at:**

Marketed Health Products Directorate (MHPD)

E-mail: [mhpd\\_dpsc@hc-sc.gc.ca](mailto:mhpd_dpsc@hc-sc.gc.ca)

Telephone: 613-954-6522

Fax: 613-952-7738

Your professional commitment in this regard has an important role in protecting the well being of your patients by contributing to early signal detection and informed drug use. A copy of this letter is also available on the Health Canada website: [http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/index\\_e.html](http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/index_e.html).

Sincerely,



Andrew Vieira, MD  
Medical Director, Inflammation  
Amgen Canada Inc.