Summary safety review - Remicade (infliximab), Humira (adalimumab), Enbrel (etanercept) and Erelzi (biosimilar etanercept) - Assessing the Potential Risk of Mycosis Fungoides

Product: Remicade (infliximab), Humira (adalimumab), Enbrel (etanercept) and Erelzi (biosimilar etanercept)

Potential Safety Issue: Mycosis fungoides, a type of cancer involving white blood cells, called T lymphocytes, which grow out of control in the skin.

Key Messages

- **Remicade, Humira, Enbrel and Erelzi belong to a class of drugs called Tumor Necrosis Factor (TNF) alpha-blockers (or anti-TNF alpha). These drugs are authorized for sale in Canada to treat adults and children who have inflammatory conditions of the skin (psoriasis, hidradenitis suppurativa), joints (rheumatoid or psoriatic arthritis, ankylosing spondylitis), intestines (Crohn's disease or ulcerative colitis), or the eyes (non-infectious uveitis).**
- **Health Canada reviewed the potential risk of mycosis fungoides, a form of lymphoma, with the use of Remicade, Humira, Enbrel or Erelzi. This review was triggered by reports of mycosis fungoides in patients treated with Remicade, which were published in the World Health Organization (WHO) Pharmaceuticals Newsletter.**
- **The Canadian product safety information for all anti-TNF alpha products have information on the risk of lymphoma. The purpose of this review was to assess whether additional regulatory actions were required in Canada specific to the risk of mycosis fungoides.**
- **Health Canada's review of the available information concluded that a link between the risk of mycosis fungoides and the use of anti-TNF alpha products could not be confirmed given limitations in the available information. As the product safety information for all anti-TNF alpha products already mentions the risk of lymphoma (which includes mycosis fungoides), no updates specific for mycosis fungoides are required at this time.**
- **Health Canada will continue to monitor safety information of all anti-TNF alpha products.**

Overview

Health Canada reviewed the potential risk of mycosis fungoides in patients treated with anti-TNF alpha products following the publication, in the WHO Pharmaceutical Newsletter, of mycosis fungoides cases resulting from the administration of infliximab (Remicade) reported by the Australian Therapeutic Goods Administration.

Mycosis fungoides is a type of cancer involving white blood cells, called T-lymphocytes, which grow out of control in the skin. It is a form of cutaneous T-cell lymphoma.

Use in Canada

- Anti-TNF alpha products are prescription drugs authorized for sale in Canada to treat adults and children with inflammation of the skin (psoriasis, hidradenitis suppurativa), joints (rheumatoid arthritis, ankylosing spondylitis or psoriatic arthritis), intestines (Crohn's disease or ulcerative colitis), or the eyes (non-infectious uveitis). This inflammation occurs when the body's immune system attacks its own tissues (autoimmune disease).
- Anti-TNF alpha products are proteins (antibodies) that block a naturally produced chemical in the body known as TNF-alpha that causes inflammation in the body.
- Anti-TNF alpha products have been marketed in Canada since 2001 under the brand names Remicade, Humira, Enbrel, Cimzia, Simponi and Erelzi (biosimilar of Enbrel).
- Cimzia and Simponi were not included in this assessment because they have only recently been authorized for sale in Canada and there have not been cases of mycosis fungoides reported with them in Canada.
- Anti-TNF alpha products are widely used. In 2019, the total number of prescriptions filled were 233,080 (Remicade), 449,085 (Humira), 144,637 (Enbrel) and 9,505 (Erelzi).

- Anti-TNF alpha products come in different strengths and formulations:
    - Remicade has been marketed in Canada since June 14, 2001. It is available as a 100 mg/vial of lyophilized powder.
    - Humira has been marketed in Canada since September 24, 2004. It comes as 50 mg/mL and 100 mg/mL solutions, packaged in prefilled syringes and prefilled pens, and as a 50 mg/mL vial.
    - Enbrel has been marketed in Canada since March 14, 2001. It comes as a 50 mg/mL solution in prefilled syringes and prefilled pens; and as a 25 mg/vial of lyophilized powder.
    - Erelzi, a biosimilar to etanercept, has been marketed in Canada since August 04, 2017. It comes as a 50 mg/mL solution, packaged in prefilled syringes and in prefilled autoinjectors.

Safety Review Findings

- Health Canada's review of information received from the manufacturers and published literature concluded that a link between mycosis fungoides and the use of anti-TNF alpha products could not be confirmed due to limitations in the cases assessed. Mycosis fungoides is a form of lymphoma, which is already included in the Canadian Product Monograph of anti-TNF alpha products.

Conclusions and Actions

- Health Canada's review of the available information concluded that a link between the risk of mycosis fungoides, a type of lymphoma, and the use of anti-TNF alpha products could not be confirmed given limitations in the available information. The product safety information for all anti-TNF alpha products already mentions the risk of lymphoma (which includes mycosis fungoides); therefore, no updates specific for mycosis fungoides are required at this time.
- Health Canada encourages consumers and healthcare professionals to report any side effects related to the use of anti-TNF alpha products and other health products to the Canada Vigilance program.
- Health Canada will continue to monitor safety information involving all anti-TNF alpha products, as it does for all health products on the Canadian market, to identify and assess potential harms. Health Canada will take appropriate and timely action should new health risks be identified.

Additional Information

- The analysis that contributed to this safety review included safety information from the manufacturers, scientific and medical literature, and information from international regulators about anti-TNF alpha products.

For additional information, contact the Marketed Health Products Directorate.