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HPRA DRUG SAFETY
NEWSLETTER

114TH EDITION

In this edition

Montelukast: New boxed warning to raise further awareness of the risk of neuropsychiatric events

Key Message

- Neuropsychiatric events such as behavioural changes, depression and suicidality have been reported in all age groups taking montelukast.
- The symptoms of neuropsychiatric events may be serious and can continue if treatment with montelukast is not withdrawn.
- If neuropsychiatric symptoms occur, treatment with montelukast should be discontinued.

Montelukast is an orally active leukotriene receptor antagonist indicated for use in the prophylaxis and treatment of asthmatic conditions.*

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC), having completed a review of data related to the known risk of neuropsychiatric events with montelukast, has recommended a new boxed warning in product information** to further raise awareness of this risk.

Neuropsychiatric events such as behavioural changes, depression and suicidality have been reported in all age groups taking montelukast. The symptoms may be serious and can continue if treatment is not withdrawn.

Healthcare professionals are advised that treatment with montelukast should be discontinued if neuropsychiatric symptoms occur during treatment.

Patients and/or caregivers should be advised to be alert for symptoms and to notify their physician if changes in behaviour occur.

A new boxed warning will be included in both the Summary of Product Characteristics (SmPC) and the package leaflet to raise further awareness.

* *Products currently authorised that contain montelukast, include, Montelair, Montelukast, and Singulair. Further details are available at www.hpra.ie.*

** *The approved product information is made up of the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) and is available at www.hpra.ie.*

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Paracetamol: Monitoring risk factors for hepatotoxicity in patients during treatment

Healthcare professionals are reminded hepatotoxicity in association with paracetamol may occur even at doses within the normal therapeutic range in patients who are at increased risk. It is important to maintain awareness of any emerging or changing risk factors during treatment with paracetamol.

Patients at an increased risk of hepatotoxicity include those who are underweight, of low body mass index, malnourished, dehydrated, chronic alcoholism or with co-existing renal or hepatic impairment. Those with conditions that may predispose to glutathione deficiency or depletion and those concomitantly taking hepatotoxic drugs are also considered at risk.

Healthcare professionals should take into consideration any emerging or changing risk factors (e.g. malnourishment, weight loss, dehydration) and maintain awareness over the course of treatment to any dose adjustment that may be warranted when prescribing or administering paracetamol.

For some patients considered to be at higher risk of hepatotoxicity, a lower starting dose, a reduction in dose and/or a reduced frequency of dosing may be appropriate. Healthcare professionals are advised to refer to the product information for the relevant paracetamol formulation.

For full information, refer to the relevant SmPC available at www.hpra.ie

Ustekinumab: New warning regarding lupus-related conditions and updated advice regarding infections

Key Message

- Lupus-related conditions have been reported in patients treated with ustekinumab, including cutaneous lupus erythematosus and lupus-like syndrome.
- If a diagnosis of a lupus-related condition is confirmed, treatment with ustekinumab should be discontinued.
- HCPs are reminded that ustekinumab is contraindicated in clinically important, active infection (e.g. active tuberculosis).

Ustekinumab (Stelara) has indications in moderate to severe plaque psoriasis in adults, adolescents, and children from the age of 6 years and older, in active psoriatic arthritis in adult patients, and in moderately to severely active Crohn's disease and ulcerative colitis in adult patients*.

Following a recent review by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) of available data, the product information** for ustekinumab will be updated to add a warning regarding lupus-related conditions and to reflect a risk of opportunistic infections.

Lupus-related conditions

Cases of lupus-related conditions have been reported in patients treated with ustekinumab. These conditions include cutaneous lupus erythematosus and lupus-like syndrome, which are now listed in product information as very rare adverse reactions.

If lesions occur, especially in sun exposed areas of the skin or if accompanied by arthralgia, the patient should seek medical attention promptly.

If the diagnosis of a lupus-related condition is confirmed, ustekinumab should be discontinued, and appropriate treatment initiated.

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Opportunistic Infections

Ustekinumab may have the potential to increase the risk of infections and reactivate latent infections. In clinical studies, serious bacterial, fungal, and viral infections have been observed in patients receiving ustekinumab.

Use is contraindicated in clinically important, active infection (e.g. active tuberculosis). Caution is advised when considering use in patients with a chronic infection or a history of recurrent infection.

An update to product information has been recommended to reflect the types of opportunistic infections that have been reported in patients treated with ustekinumab. These include reactivation of tuberculosis, other opportunistic bacterial infections (including atypical mycobacterial infection, listeria meningitis, pneumonia legionella, and nocardiosis), opportunistic fungal infections, opportunistic viral infections (including encephalitis caused by herpes simplex 2), and parasitic infections (including ocular toxoplasmosis).

Healthcare professionals are reminded that prior to initiating treatment with ustekinumab, patients should be evaluated for tuberculosis infection. Treatment of latent tuberculosis infection should be initiated prior to administering ustekinumab. Anti-tuberculosis therapy should be considered prior to initiation of ustekinumab in patients with a history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Patients receiving ustekinumab should be monitored closely for signs and symptoms of active tuberculosis during and after treatment.

As already recommended in the product information, patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur.

If a patient develops a serious infection, the patient should be closely monitored and ustekinumab should not be administered until the infection resolves.

* *Currently authorised ustekinumab products include, Stelara. Refer to product information for further details on authorised indications, available at www.hpra.ie.*

** *The approved product information is made up of the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) and is available at www.hpra.ie.*

Venlafaxine: Updated warning and advice on complex cases involving overdose and severe poisoning

Key Message

- Overdose with venlafaxine, including cases with a fatal outcome, have been reported predominantly in combination with alcohol and/or other medicinal products.
- Patients treated with venlafaxine should be advised not to use alcohol, considering its CNS-effects and potential of clinical worsening of psychiatric conditions, and for adverse interactions with venlafaxine including CNS depressant effects.
- Prescriptions for venlafaxine should be written for the smallest quantity consistent with good patient management to reduce the risk of overdose.

Venlafaxine is a dual-acting serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor (SNRI). It is authorised in Ireland, under various brand names, for the treatment of depression, prevention of relapse and prevention of recurrence of depression, and treatment of anxiety and panic-related disorders*.

Following a periodic safety review of available data from the literature and spontaneous reports, the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) have recommended an update to product information** to expand advice and warnings regarding the established risk for serious outcomes due to suicide attempts, misuse, overdoses, and severe poisoning.

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The recommendations reflect the complexity in cases of suicidal/suicide events, that also involve severe poisoning with venlafaxine, and often combine poisoning involving alcohol and/or other medicines or other substances, or underlying disease (e.g. major depression).

Patients should be advised not to use alcohol, considering its central nervous system (CNS) effects and potential of clinical worsening of psychiatric conditions, and the potential for adverse interactions with venlafaxine including CNS depressant effects.

Healthcare professionals are advised to prescribe venlafaxine for the smallest quantity consistent with good patient management, to reduce the risk of overdose.

Overdose with venlafaxine has been reported predominantly in combination with alcohol and/or other medicinal products including cases with a fatal outcome.

Severe poisoning symptoms may occur in adults after intake of approximately 3 grams of venlafaxine.

Complex emergency treatment and monitoring may be required. In the event of suspected overdose involving venlafaxine, prompt contact with the National Poisons Information Centre of Ireland is recommended.

* *Currently authorised venlafaxine-containing medicines include, Efexor XL, Ireven, Majoven XL, Vedixal, Vedixal XL, Venex XL, Venlablue, Venlafex XL, Venlatev, and Vensir XL. Refer to product information for further details on authorised indications, available at www.hpra.ie.*

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Direct Healthcare Professional Communications published on the HPRA website since the last Drug Safety Newsletter

PRODUCT	SAFETY ISSUE
Topamax (Topiramate)	New restrictions to prevent exposure during pregnancy
Omega-3-acid ethyl ester medicines	Dose-dependent increased risk of atrial fibrillation in patients with established cardiovascular diseases or cardiovascular risk factors

Reporting suspected adverse reactions

Healthcare professionals are encouraged to report suspected adverse reactions to the HPRA via the available options at http://www.hpra.ie/report, which include an online report form. All reports submitted to the HPRA are reviewed and stored on the HPRA's national adverse reaction database. They are subsequently submitted to the EMA's EudraVigilance database where they are available for analysis and to support early detection and monitoring of possible safety signals. Reporting suspected adverse reactions, even those known to occur in association with a medicine, adds to knowledge about the frequency and severity of these reactions and can help to identify patients who are most at risk.

A privacy notice relating the to the processing of personal data collected by the HPRA in relation to adverse reaction reports is available on the HPRA website

Correspondence/comments should be sent **by email only** to the Pharmacovigilance Section, Health Products Regulatory Authority, medsafety@hpra.ie.

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