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HPRA DRUG SAFETY NEWSLETTER

121ST EDITION

In this edition

Fezolinetant: Risk of drug-induced liver injury and new recommendations on monitoring of liver function before and during treatment

Key Messages

- **Serious liver injury** has been observed with fezolinetant (Veoza▼).
- **Liver function tests (LFTs)**: LFTs must be performed prior to initiation of fezolinetant. Treatment with fezolinetant must not be initiated if serum alanine aminotransferase (ALT) or serum aspartate aminotransferase (AST) levels are ≥2x upper limit of normal (ULN) or if total bilirubin levels are ≥2x ULN.
- **Monitoring requirements**: During the first three months of treatment, monthly LFTs must be performed, and thereafter based on clinical judgement. LFTs must also be performed when symptoms suggestive of liver injury occur.
- **Treatment with fezolinetant must be discontinued if**:
  - Transaminase elevations are ≥3x ULN with: total bilirubin >2x ULN OR if patients develop symptoms of liver injury;
  - Transaminase elevations >5x ULN.
- **Continued monitoring**: Monitoring of LFTs should be maintained until normalisation.
- **Need for medical attention**: Patients must be advised to immediately seek medical attention if they experience signs or symptoms that may suggest liver injury such as fatigue, pruritus, jaundice, dark urine, pale faeces, nausea, vomiting, decreased appetite and/or abdominal pain.

1 Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland.
T: +353 1 676 4971 E: medsafety@hpra.ie www.hpra.ie

Fezolinetant is a neurokinin-3 receptor antagonist. Medicines containing fezolinetant* are indicated for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause. Fezolinetant is available in Ireland under the brand name Veoza and is subject to additional monitoring*.

Recently identified safety information on liver injury prompted an EU-wide review of data of the potential of fezolinetant to cause drug-induced liver injury (DILI). The review was undertaken by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC). Information from all available sources, including suspected adverse reaction reports and studies published in the scientific literature, was considered.

Elevations in serum ALT and AST were already observed in clinical trials with fezolinetant and are already described in product information*.

However, the review identified that serious cases with elevations of ALT and/or AST (>10x ULN) with concurrent elevations in bilirubin and/or alkaline phosphatase (ALP) were reported post-marketing. In some cases, elevated LFTs were associated with signs or symptoms suggestive of liver injury such as fatigue, pruritus, jaundice, dark urine, decreased appetite or abdominal pain.

Since fezolinetant is indicated for a condition in otherwise healthy women, the risk of serious liver injury may significantly affect its benefit-risk balance. Consequently, exposure to the substance should be avoided in women at higher risk for liver disease and early recognition of potential liver injury is essential. Therefore, LFTs should be performed before treatment initiation. Treatment should not be initiated if ALT and/or AST levels are ≥2x ULN or bilirubin levels are ≥2x ULN.

Elevated liver function tests and/or symptoms suggestive of liver injury were generally reversible on discontinuation of therapy. During the first three months of treatment, monthly LFTs must be performed, and thereafter based on clinical judgement. Throughout treatment, LFTs must be performed if symptoms suggestive of liver injury occur. Treatment should be discontinued in the following situations:

- Transaminase elevations are ≥3x ULN with: total bilirubin >2x ULN OR patients develop symptoms of liver injury
- Transaminase elevations are >5x ULN

Monitoring of liver function should be maintained until they have normalised.

Patients should be advised to be vigilant for signs and symptoms of potential liver injury, including fatigue, pruritus, jaundice, dark urine, pale faeces, nausea, vomiting, decreased appetite and/or abdominal pain, and to seek immediate medical attention if such symptoms arise. The summary of product characteristics and package leaflet of Veoza* have been updated in accordance with the new risk information and recommendations described above. Drug-induced liver injury has also been included as an adverse drug reaction with the frequency "not known" since the frequency cannot be calculated from the data provided.

A Direct Healthcare Professional Communication (DHPC) has been issued to inform healthcare professionals of these updates.

* *Further details on products containing fezolinetant, are available from www.hpra.ie. Healthcare professionals are asked to report any suspected adverse drug reactions at www.hpra.ie.*

Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland.
T: +353 1 676 4971 E: medsafety@hpra.ie **www.hpra.ie**

Enzalutamide and digoxin: Laboratory test interference leading to falsely elevated digoxin plasma levels and a reminder of the existing interaction

Key Messages

Chemiluminescent microparticle immunoassay (CMIA) interference:

- Falsely elevated serum digoxin levels detected using CMIA have been identified in patients treated with enzalutamide, even in the absence of digoxin treatment.
- Results of serum digoxin levels obtained by CMIA should be interpreted with caution in patients taking enzalutamide.
- Confirmation by another type of assay is recommended before determining the need for any discontinuation, or decrease in dose, of digoxin.

Reminder of existing enzalutamide-digoxin interaction:

- Healthcare professionals are reminded that enzalutamide may inhibit the efflux transporter P-glycoprotein (P-gp) which could lead to increased plasma levels of digoxin, a P-gp substrate.
- Digoxin should be used with caution when administered concomitantly with enzalutamide and may require dose adjustment to maintain optimal plasma concentrations.

Enzalutamide* is an androgen receptor inhibitor indicated in the treatment of certain types of prostate cancer. Digoxin* is indicated in the management of chronic cardiac failure when the dominant problem is systolic dysfunction, and in the management of certain supraventricular arrhythmias, particularly chronic atrial flutter and fibrillation.

Current product information for enzalutamide highlights that it may be an inhibitor of the efflux transporter P-glycoprotein (P-gp), which may lead to increased plasma levels of medicines that are substrates of P-gp. It is advised that medicinal products with a narrow therapeutic range that are substrates for P-gp, including digoxin, should be used with caution when administered concomitantly with enzalutamide. A dose adjustment may be required to maintain optimal plasma concentrations.

The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) recommended a further update to product information following a routine periodic review of available information. The update reflects that enzalutamide may interfere with the CMIA laboratory test method, leading to falsely elevated serum digoxin level results in patients taking enzalutamide, regardless of whether the patient is taking digoxin. Therefore, in cases of doubtful results, it is advised that serum digoxin levels obtained by CMIA should be interpreted with caution in patients taking enzalutamide and confirmed by another type of assay without known interference before determining the need for any discontinuation of or decrease in dose of digoxin in patients taking enzalutamide.

A Direct Healthcare Professional Communication (DHPC) has been distributed by the marketing authorisation holder in Ireland to medical laboratory personnel in relation to this update.

* *Further details on products containing enzalutamide (Xtandi) and digoxin (Lanoxin) are available at www.hpra.ie.*

Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland.
T: +353 1 676 4971 E: medsafety@hpra.ie www.hpra.ie

Glucagon-like peptide-1 (GLP-1) analogues: Highlight and reminder of certain safety aspects

Key Messages

- **Increased risk for non-arteritic ischemic optic neuropathy (NAION) with semaglutide.** A sudden loss of vision or rapidly worsening eyesight should lead to ophthalmological examination and semaglutide should be discontinued if NAION is confirmed.
- **Cases of pulmonary aspiration** due to residual gastric contents have been reported in patients receiving GLP-1 analogues undergoing general anaesthesia or deep sedation, which should be considered before any surgeries or procedures.
- **Acute pancreatitis** has been observed with the use of GLP-1 analogues. Treatment should be discontinued if symptoms occur.
- **The use of GLP-1 analogues in pregnancy.** GLP-1 analogues should not be used during pregnancy or are not recommended for use during pregnancy.

Background

Glucagon-like peptide-1 (GLP-1) analogues such as semaglutide*, dulaglutide*, exenatide*, liraglutide*, lixisenatide* and tirzepatide* are used along with diet and physical activity for the treatment of type 2 diabetes and for weight management. This article provides reminders for healthcare professionals on some recent safety issues related to GLP-1 analogue medicines. For specific advice on each medicine, please consult its product information*.

NAION with semaglutide

NAION (non-arteritic ischemic optic neuropathy) is a serious ocular condition that compromises the blood supply to the optic nerve, potentially leading to sudden unilateral vision loss.

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) reviewed all available information on NAION with semaglutide, including data from non-clinical studies, clinical trials, post-marketing surveillance and the medical literature. The PRAC concluded that based on the available evidence, NAION is considered a very rare adverse reaction of semaglutide. Results from several large epidemiological studies suggest that exposure to semaglutide in adults with type 2 diabetes is associated with an approximately two-fold increase in the risk of developing NAION, corresponding to approximately one additional case of NAION per 10,000 person-years of treatment.

Advice for healthcare professionals:

- If patients experience a sudden loss of vision or rapidly worsening eyesight during treatment with semaglutide, they should contact their doctor without delay.
- A sudden loss of vision should lead to ophthalmological examination.
- Treatment with semaglutide should be discontinued if NAION is confirmed.
- There is no identified time interval for when NAION may develop following initiation of treatment.

Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland.
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Aspiration in association with general anaesthesia or deep sedation

Delayed gastric emptying is a known effect of GLP-1 analogues and is listed in the product information for different GLP-1 analogues. Cases of pulmonary aspiration have been reported in patients undergoing general anaesthesia or deep sedation.

Following a review of available information on GLP-1 analogues and aspiration, given the known action of delayed gastric emptying and the presence of clinical trial cases and post-marketing cases, the EMA's PRAC recommended an update to the product information to highlight to healthcare professionals the potential consequence of delayed gastric emptying.

The product information for GLP-1 analogues* has been updated to advise healthcare professionals that the risk of residual gastric content due to delayed gastric emptying should be considered before performing procedures under general anaesthesia or deep sedation.

A warning to patients has also been included in the package leaflet*, advising them to inform their doctor that they take these medicines if scheduled to undergo surgery under anaesthesia.

Gastrointestinal effects

Use of GLP-1 analogues may be associated with gastrointestinal adverse reactions. This should be considered when treating patients with impaired renal function as nausea, vomiting, and diarrhoea may cause dehydration which could cause a deterioration of renal function.

Acute pancreatitis

Healthcare professionals are reminded that acute pancreatitis has been observed with the use of GLP-1 analogues. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, GLP-1 analogues should be discontinued; if confirmed, GLP-1 analogues should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

The use of GLP-1 analogues in pregnancy

Healthcare professionals are reminded that GLP-1 analogues should not be used (semaglutide, liraglutide, exenatide and lixisenatide) or are not recommended (dulaglutide and tirzepatide) during pregnancy. There is substance-specific advice relating to the use of GLP-1 analogues in pregnancy, contraception and the use in women of childbearing potential who are considering becoming pregnant in the specific medicine's product information*.

* *Further details, such as the product information for products containing semaglutide, dulaglutide, exenatide, liraglutide, lixisenatide and tirzepatide are available at www.hpra.ie.*

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Product information updates recommended by the Pharmacovigilance Risk Assessment Committee

The HPRA highlights a selection of recommendations made by the PRAC to update product information for medicines in clinical use. The approved product information comprises the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) and is available at www.hpra.ie. The PRAC, in which the HPRA participate, is responsible for assessing and monitoring the safety of medicines. Healthcare professionals are reminded to check the HPRA or EMA websites regularly for current product information concerning medicines.

Macrogol 3350 with electrolytes (oral use): seizure and oesophageal rupture when used in bowel preparation.

These updates affect products indicated for bowel preparation.

Seizures:

- Cases of seizures associated with the use of macrogol 3350 with electrolytes for bowel preparation were observed in patients with and without a prior history of seizures. These cases were mostly associated with electrolyte abnormalities, such as severe hyponatraemia.
- Caution is advised when prescribing macrogol 3350 with electrolytes in patients with a history of seizures, at increased risk of seizures or those at risk of electrolyte disturbances.
- In the event of neurological symptoms, fluid and electrolyte abnormalities should be corrected.

Oesophageal Rupture (Boerhaave's Syndrome):

- Cases of oesophageal rupture associated with excessive vomiting after intake of macrogol 3350 with electrolytes for bowel preparation has been reported post-marketing, mostly in elderly patients.
- Patients should be advised to discontinue use and seek immediate medical assistance if they experience incoercible vomiting and subsequent chest, neck and abdominal pain, dysphagia, hematemesis, or dyspnoea.

Trimethoprim: Drug reaction with Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and eosinophilia and systemic symptoms (DRESS)

Trimethoprim-containing medicines are indicated for the treatment of certain urinary and respiratory tract infections and for the prophylaxis of recurrent urinary tract infections.

- Product information updates for trimethoprim-containing medicines have been recommended to reflect that cases of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in association with trimethoprim treatment.
- Patients should be advised of the signs and symptoms and monitored closely for skin reactions.
- If signs and symptoms suggestive of these reactions appear, trimethoprim should be withdrawn immediately and an alternative considered (as appropriate).
- If the patient has developed a serious reaction, such as SJS, TEN, or DRESS, with the use of trimethoprim, the treatment must not be restarted in this patient at any time.

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Domperidone: Risk of acute hypertension episodes in patients with phaeochromocytoma

Domperidone-containing medicines are indicated for the relief of the symptoms of nausea and vomiting.

- A new warning in product information will reflect that domperidone-containing products are contraindicated in patients with confirmed or suspected pheochromocytoma.
- The use of domperidone-containing medicines is not recommended in these patients due to the risk of severe hypertension episodes.

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

PRODUCT	SAFETY ISSUE
Clozapine	Revised recommendations for routine blood count monitoring for the risk of agranulocytosis.
Finasteride, dutasteride	New measures to minimise the risk of suicidal ideation.
Ixchiq (Chikungunya vaccine (live-attenuated))	Lifting of temporary contraindication in adults 65 years and older; warning on severe adverse reactions, including encephalitis.
Enzalutamide and digoxin	Enzalutamide laboratory test interference leading to falsely elevated digoxin plasma levels
Caspofungin	Avoid use of polyacrylonitrile membranes during continuous renal replacement therapy.
Crysvita (burosumab)	Risk of severe hypercalcaemia.
Tranexamic acid intravenous formulations	Serious including fatal adverse reactions due to inadvertent intrathecal administration

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 to the processing of personal data collected by the HPRA in relation to adverse reaction reports is available at www.hpra.ie

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