March 2023

HPRA DRUG SAFETY NEWSLETTER

111TH EDITION

In this edition

Levothyroxine: Biotin interference with thyroid function tests, and drug-drug interaction between levothyroxine and St. John's Wort and proton-pump inhibitors (PPIs)

Levothyroxine* is a synthetic thyroid hormone authorised in adults and children for the treatment of conditions associated with hypothyroidism, suppression therapy for thyroid carcinoma, and for diagnostic use for thyroid suppression testing.

Following a recent review by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) of available data, the product information** of levothyroxine will be updated with new warnings relating to biotin interference with thyroid function tests and drug-drug interactions with proton-pump inhibitors (PPI) and St. John's Wort. Further information on these changes is provided below.

Biotin Interference with Thyroid Function Tests

Biotin may interfere with thyroid immunoassays that are based on a biotin/streptavidin interaction. These test methods are commonly used in clinical practice for the measurement of thyroid function and therapeutic drug monitoring for the adjustment of levothyroxine dosage. This may result in falsely decreased or increased test results depending on the assay design and a potential for inappropriate patient management or misdiagnosis. Patients should be routinely asked about biotin use before ordering thyroid function tests. If a patient is taking biotin, inform the laboratory personnel before ordering the tests, as alternative assays might be available. Care should be taken when interpreting laboratory-based thyroid function tests particularly if results do not match the clinical presentation and/or other investigations. Alternative tests not susceptible to biotin interference should be used, if available. Patients should be advised to consult their doctor if they are taking or have recently taken biotin. They should also be aware that other products that they may take, such as multivitamins or supplements for hair, skin, and nails could also contain biotin and affect the results of their thyroid function tests. A DHPC with further information has been circulated to healthcare professionals (see DHPC).

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Drug interactions, St. John's Wort and proton-pump inhibitors (PPIs)

Co-administration of levothyroxine with PPIs (such as omeprazole, esomeprazole, pantoprazole, rabeprazole, and lanzoprazole) may decrease the absorption of thyroid hormones due to suppression of gastric acid secretion caused by PPIs. Regular monitoring of thyroid function and clinical monitoring is recommended during concomitant treatment. It may be necessary to increase the dose of thyroid hormones.

Products containing St John's Wort (Hypericum perforatum), which is a potent inducer of several liver metabolic enzymes, may increase hepatic clearance of levothyroxine, resulting in reduced serum concentrations of thyroid hormone. Patients may require an increase in their dose of thyroid hormone if these drugs are given concurrently.

Key Message

- Biotin may interfere with thyroid immunoassays based on a biotin/streptavidin interaction. This may result in falsely decreased or increased test results and potentially inappropriate patient management or misdiagnosis.
- Care should be taken when interpreting laboratory-based thyroid function tests particularly if results of thyroid function tests do not match the clinical presentation.
- Routinely ask patients about biotin use before ordering thyroid function tests. Patients should consult their doctor if they are taking or have recently taken biotin. They should also be made aware that, other products that they may take, could also contain biotin and affect the results of their thyroid function tests.
- Drug-drug interactions between levothyroxine and St. John's Wort and between levothyroxine and proton-pump inhibitors (PPIs) may alter levels of thyroid hormones. Regular monitoring of thyroid function and clinical monitoring is recommended during concomitant treatment of these drugs.

* *Further details on levothyroxine-containing medicines 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.*

Levonorgestrel-containing products: Factors associated with increased risk of expulsion and update on risks associated with intrauterine exposure

Levonorgestrel-containing intrauterine devices (IUD)* are authorised for use in Ireland as contraception (Kyleena 19.5 mg and Jaydess 13.5 mg IUD); and as contraception, treatment for idiopathic menorrhagia, and protection from endometrial hyperplasia during oestrogen replacement therapy (Mirena 52 mg IUD).

Following a recent review by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) of the available data, the product information** for levonorgestrel-containing IUDs will be updated to reflect the increased risk of expulsion in women with heavy menstrual bleeding and in those with a higher-than-normal body mass index (BMI). The product information will also be updated to include a warning on virilising effects in a female foetus in context of intrauterine exposure. Further information on these changes is provided below.

Risk of Expulsion

There is an increased risk of expulsion of levonorgestrel-containing IUDs in women with a history of heavy menstrual bleeding (including women who use IUD for treatment for heavy menstrual bleeding) and in women with greater than normal BMI at the time of insertion. The risk increases gradually with increasing BMI. Woman should be counselled

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on possible signs of expulsion, including on how to check the threads of their product, and to contact a healthcare professional if the threads cannot be felt. A barrier contraceptive (such as a condom) should be used until the location of the IUD is confirmed. Partial expulsion may decrease the effectiveness.

Intrauterine Exposure

The use of levonorgestrel-containing IUDs during an existing or suspected pregnancy is already contraindicated, and product information includes advice in relation to removal of the system. In addition, product information has now been updated to reflect that an increased risk of virilising effects in a female foetus due to intrauterine exposure to levonorgestrel cannot be excluded. There have been isolated cases of masculinization of the external genitalia of the female foetus following local exposure to levonorgestrel during pregnancy with an IUD in place.

Key Message

- There is an increased risk of expulsion in women with a history of heavy menstrual bleeding (including women who use IUD for treatment of heavy menstrual bleeding) and women with greater than normal BMI at the time of insertion
- Counsel women on signs of expulsion and on the need to use barrier contraceptive (such as a condom) until the location of the IUD is confirmed

* *Further details on levonorgestrel-containing medicines 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.*

IMBRUVICA® (ibrutinib): New risk minimisation measures, including dose modification recommendations, due to increased risk of serious cardiac events

Imbruvica is authorised in Ireland and across the EU as a single agent or in combination with other therapeutics for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL), chronic lymphocytic leukaemia (CLL), or Waldenström's macroglobulinaemia (WM).*

Based on an assessment of available data on the cardiotoxicity of ibrutinib, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has recommended further measures to minimise risks and updates to product information**.

The assessment of data from a randomised controlled trial pool of ibrutinib showed an almost 5-fold higher crude incident of sudden cardiac death, sudden death, and cardiac death in the ibrutinib arm (11 cases; 0.48%) versus the comparator arm (2 cases; 0.10%). When adjusted for exposure, a 2-fold increase in the incidence rate (EAIR, expressed as number of subjects with events divided with patient-months at risk) of events of sudden cardiac death, sudden death or cardiac death was observed in the ibrutinib arm (0.0002) versus the comparator arm (0.0001) (see Direct Healthcare Professional Communication for further details).

Based on the available data, the PRAC consider that patients with advanced age, Eastern Cooperative Oncology Group (ECOG) performance status ≥2, or cardiac co-morbidities may be at greater risk of events including sudden fatal cardiac events.

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Further Measures to Minimise Risk of Serious Cardiac Events

Appropriate clinical evaluation of cardiac history and function should be performed prior to initiating ibrutinib.

Patients should be carefully monitored during treatment for signs of clinical deterioration of cardiac function and clinically managed. Consider further evaluation (e.g., ECG, echocardiogram), as indicated for patients in whom there are cardiovascular concerns.

For patients with relevant risk factors for cardiac events, carefully assess benefit/risk before initiating treatment with ibrutinib; alternative treatments may be considered.

Product information has been updated to include a warning in section 4.4 of the SmPC and cardiac arrest has been added as an adverse drug reaction with a frequency of uncommon in section 4.8 of the SmPC.

Product information has also been updated with advice on dose modification for patients experiencing cardiac events.

Healthcare professionals can reference the product information of Imbruvica* for full details of the revised measures as well as all current warnings and precautions for use.

Key Message

- Fatal and serious cardiac arrhythmias and cardiac failure have been reported in patients treated with ibrutinib.
- Patients with advanced age, Eastern Cooperative Oncology Group (ECOG) performance status ≥2, or cardiac co-morbidities may be at greater risk of events including sudden fatal cardiac events.
- Appropriate clinical evaluation of cardiac history and function should be performed prior to initiating treatment.
- Patients should be carefully monitored during treatment for signs of clinical deterioration of cardiac function and clinically managed.
- For patients with relevant risk factors for cardiac events, carefully assess benefit/risk before initiating treatment; alternative treatment may be considered.
- Product information has been updated with new recommendations regarding dose modification in case of cardiac failure and cardiac arrhythmias.
- Further details on measures to minimise risk of serious cardiac events are available in a recent DHPC and the product information of Imbruvica.

* *Imbruvia is indicated as a single agent for the treatment of adult patients with relapsed or refractory MCL; as a single agent or in combination with rituximab or obinutuzumab or venetoclax for the treatment of adult patients with previously untreated CLL; as a single agent or in combination with bendamustine and rituximab for the treatment of adult patients with CLL who have received at least one prior therapy; as a single agent for the treatment of adult patients with WM who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy. Ibrutinib in combination with rituximab is also indicated for the treatment of adult patients with WM.*

Further details are available from product information at www.hpra.ie and www.ema.europa.eu.

** *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 or www.ema.europa.eu.*

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Product information updates recommended by Pharmacovigilance Risk Assessment Committee

The HPRA is highlighting a selection of recommendations, made by the PRAC, to update product information for medicines in clinical use. The PRAC, in which the HPRA participate, are responsible for assessing and monitoring the safety of medicines. HCPs are reminded to regularly check the HPRA or EMA websites for current product information concerning medicines.

Donepezil: Potential risk of QTc prolongation and Torsade de Pointes in patients prescribed donepezil-containing medicines

Donepezil is licenced for the symptomatic treatment of mild to moderately severe Alzheimer's dementia.

- Product information for donepezil-containing medicines has been updated to reflect post-marketing reports of QTc interval prolongation and Torsade de Pointes in patients prescribed donepezil.
- Caution is advised in patients with pre-existing or family history of QTc prolongation, in patients treated with drugs affecting the QTc interval, or in patients with relevant pre-existing cardiac disease (e.g. uncompensated heart failure, recent myocardial infarction, bradyarrhythmias), or electrolyte disturbances (hypokalaemia, hypomagnesaemia). Clinical monitoring (ECG) may be required.
- Caution is also advised when donepezil is used in combination with medicinal products known to prolong the QTc interval and clinical monitoring (ECG) may be required. Examples include class IA and class III antiarrhythmics, and certain antidepressants, antibiotics or antipsychotics.

Guanfacine (Intuniv▼): Updated warnings concerning potential for suicide-related events and aggressive behaviour

Intuniv is licenced for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents 6-17 years old for whom stimulants are not suitable, not tolerated or have been shown to be ineffective

- Product information has been updated to reflect that suicide-related events (including suicidal ideation, attempts and completed suicide) have been reported in patients treated with guanfacine. In most cases patients had underlying psychiatric disorders.
- Caregivers and physicians should monitor patients for signs of suicide-related events, including at dose initiation/optimisation and drug discontinuation.
- Patients and caregivers should be encouraged to report any distressing thoughts or feelings at any time to their healthcare professional.
- Product information has been also updated to reflect that aggressive behaviour or hostility has been reported. Patients treated with guanfacine should be monitored for the appearance of aggressive behaviour or hostility.

Lisdexamphetamine: risk of QTc interval prolongation

Lisdexamphetamine is licensed as part of a comprehensive treatment programme for attention deficit hyperactivity disorder (ADHD) in children aged 6 years and over when response to previous methylphenidate treatment is considered clinically inadequate.

- The product information for lisdexamphetamine-containing medicines contains warnings on the potential for cardiovascular adverse events in patients taking central nervous system stimulants. Following a review of available data, the PRAC recommended the inclusion of an additional warning concerning QTc interval prolongation.
- The SmPC has been updated to reflect that lisdexamfetamine has been shown to prolong the QTc interval in some patients. It should be used with caution in patients with prolongation of the QTc interval, in patients treated with drugs affecting the QTc interval, or in patients with relevant pre-existing cardiac disease or electrolyte disturbances.

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

PRODUCT	SAFETY ISSUE
ADAKVEO (Crizanlizumab)	Study shows no superiority of crizanlizumab over placebo
Levothyroxine containing products	Biotin interference with thyroid function tests
Zolgensma (Onasemnogene aberparvovec)	Fatal cases of acute liver failure
Bendamustine Accord 25mg/ml concentrate for solution for infusion	Potential risk of medication errors when diluting higher strength solution newly launched in Ireland.

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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