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Use of Lemtrada (alemtuzumab) restricted while European Medicines Agency (EMA) review is ongoing

The Pharmacovigilance Risk Assessment Committee ([PRAC](#)) of the EMA has commenced a review of Lemtrada which is used to treat adult patients with active relapsing remitting multiple sclerosis. The review was commenced following identification of new safety information on alemtuzumab from use in clinical practice, including cardiovascular reactions and immune-mediated reactions.

While the review is ongoing, temporary measures to restrict the use of Lemtrada have been recommended by PRAC:

Lemtrada should only be initiated in adults with highly active relapsing remitting multiple sclerosis despite a full and adequate course of treatment with at least other two disease-modifying treatments or where all other disease-modifying treatments are contraindicated or otherwise unsuitable.

Patients currently being treated with Lemtrada who are benefiting from it may continue treatment in consultation with their prescribing doctor.

New safety information identified for alemtuzumab included individual cases of cardiovascular reactions, mostly occurring within 1-3 days of treatment with alemtuzumab. Reported events in these cases included myocardial infarction, ischaemic and haemorrhagic cerebrovascular accident, cervicocephalic arterial dissection and pulmonary alveolar haemorrhage. The mechanism for these reactions is not known. Cases of autoimmune hepatitis and haemophagocytic lymphohistiocytosis (a syndrome of excessive immune activation) have also been reported in patients who have received alemtuzumab. Additionally, there have been reports of severe neutropenia within 2 months of receiving alemtuzumab. Some cases have been fatal.

In addition to restricting use of alemtuzumab while the review is ongoing, the PRAC has also recommended that the product information should be updated with advice in relation to monitoring for cardiovascular reactions, autoimmune hepatitis, haemophagocytic lymphohistiocytosis, and neutropenia.

Further information will become available as the review progresses.

Advice to Healthcare Professionals

- New treatment with Lemtrada should only be initiated in adults with highly active relapsing-remitting multiple sclerosis despite a full and adequate course of treatment with at least two other disease-modifying treatments or where all other disease-modifying treatments are contraindicated or otherwise unsuitable.
- Patients currently being treated with Lemtrada and who are benefiting from treatment may continue treatment in consultation with their prescribing doctor.

- For patients currently being treated with Lemtrada, vital signs, including blood pressure, should be monitored before and during intravenous infusion. If clinically relevant changes are observed, discontinuation of infusion and additional monitoring, including ECG, should be considered. Patients should be advised to seek medical help right away if they develop cardiovascular, cerebrovascular or respiratory symptoms or haemoptysis.
- Liver function tests should be carried out before and during treatment. Patients should be advised to seek medical attention if they develop any symptoms of liver inflammation.
- Patients who develop signs of pathological immune activation, such as fever, lymphadenopathy, unusual bruising or rash should be evaluated immediately and a diagnosis of haemophagocytic lymphohistiocytosis considered. This syndrome may occur up to four years after the start of treatment.
- Cases of neutropenia have been reported within 2 months of treatment with alemtuzumab. As currently recommended in the product information, complete blood counts with differential WBC should be obtained prior to treatment and at monthly intervals until 48 months after the last infusion to monitor for cytopenias. If cytopenia is confirmed, appropriate medical intervention should be promptly initiated including referral to a specialist.
- Further information will be available following a detailed review of the benefit-risk balance of Lemtrada in the approved indication, including whether any further risk minimisation measures should be implemented.

Key Message

Following new safety information identified during routine monitoring, PRAC has commenced a review of the efficacy and safety of alemtuzumab, to determine whether changes to the authorised use are warranted.

While the review is on-going, new treatment with Lemtrada should only be initiated in adults with highly active relapsing-remitting multiple sclerosis despite a full and adequate course of treatment with at least two other disease-modifying treatments or where all other disease modifying treatment are contraindicated or otherwise unsuitable.

Patients currently being treated with Lemtrada and who are benefitting from treatment may continue treatment in consultation with their prescribing doctor.

PRAC has also recommended that the product information should be updated to inform healthcare professionals and patients in relation to vascular reactions including ischaemic and haemorrhagic stroke, vertebral and carotid arterial dissection, pulmonary alveolar haemorrhage, and myocardial infarction, immune mediated reactions including autoimmune hepatitis and haemophagocytic lymphohistiocytosis, and severe neutropenia.

Further information will be available following an in-depth review of the benefit-risk balance of Lemtrada in the approved indication, including whether any further risk minimisation measures should be implemented.

Any suspected adverse reactions should be reported to the HPRA using the available options (www.hpra.ie).

This information has also been communicated to relevant healthcare professionals through a Direct Healthcare Professional Communication (DHPC) circulated by the Marketing Authorisation Holder (MAH), following approval by the HPRA.

* Further information is available on www.hpra.ie and www.ema.europa.eu

SGLT-2 inhibitors and risk of Fournier's Gangrene (necrotising fasciitis of the perineum)

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has concluded its review of the risk of Fournier's gangrene associated with sodium-glucose co-transporter 2 (SGLT-2) inhibitors*, which are indicated in adults for the treatment of Type 2 diabetes, as monotherapy or in combination with other diabetes medicines.

Fournier's gangrene is a urological emergency, characterised by a rapidly progressive necrotising infection of the external genitalia, perineum and perianal region, requiring treatment with antibiotics and immediate surgical intervention. Although diabetes mellitus is a risk factor for the development of Fournier's gangrene, post-marketing reports of suspected adverse reactions (spontaneous reports) indicate a possible association between treatment with an SGLT-2 inhibitor and development of Fournier's gangrene. Fournier's gangrene is known to occur almost exclusively in men however in association with an SGLT-2 inhibitor, it has also been reported in women.

Based on the assessment of the available data sources (spontaneous reports and literature), the PRAC considered that the most recent data demonstrates a possible causal association between Fournier's gangrene and an SGLT-2 inhibitor. The PRAC concluded that the benefit-risk balance of SGLT-2 inhibitor-containing products remains favourable, subject to amendments to the product information.

Advice to Healthcare Professionals

- Post-marketing cases of Fournier's gangrene (necrotising fasciitis of the perineum) have been associated with the use of an SGLT-2 inhibitor.
- Fournier's gangrene is a rare but serious and potentially life-threatening infection that requires urgent surgical intervention and antibiotic treatment.
- Fournier's gangrene may be preceded by uro-genital infection or perineal abscess.
- Patients should be advised of the signs and symptoms of Fournier's gangrene which include pain, tenderness, erythema or swelling in the genital or perineal area accompanied by fever or malaise and to seek urgent medical attention if any of these symptoms are experienced.
- Healthcare professionals should be aware that if Fournier's gangrene is suspected, treatment with an SGLT-2 inhibitor should be stopped and treatment for Fournier's gangrene should commence promptly (antibiotics and surgical debridement).
- This information has also been communicated through a Direct Healthcare Professional Communication ([DHPC](#)), circulated by the Marketing Authorisation Holders, following approval by the HPRa.

Key Message

Post marketing reports in Europe and across the world have been received indicating an association between an SGLT-2 inhibitor and Fournier's gangrene (necrotising fasciitis of the perineum).

Patients should be warned of the signs and symptoms of Fournier's gangrene and advised to seek urgent medical attention if any are experienced.

Treatment with an SGLT-2 inhibitor should be stopped if Fournier's gangrene is suspected and treatment, including antibiotics and surgical debridement, should be started promptly.

The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for these products has been updated.

Any suspected adverse reactions should be reported to the HPRa through the available options (www.hpra.ie).

**SGLT-2 inhibitor-containing products include Forxiga, Xigduo, Jardiance, Synjardy, Steglatro, Invokana and Vokanamet. Further details are available on www.hpra.ie and www.ema.europa.eu*

Cobicistat boosted darunavir and elvitegravir: avoid use in pregnancy due to potential risk of virological failure in the second and third trimester

Pharmacokinetic data show exposure of darunavir boosted with cobicistat and elvitegravir boosted with cobicistat to be lower during the second and third trimesters of pregnancy compared to postpartum. Low darunavir or elvitegravir exposure may be associated with an increased risk of virological failure. Virological failure increases the risk of mother to child transmission of HIV infection.

Lower exposure in pregnancy

Cobicistat boosted darunavir

Pharmacokinetic data from a Phase 3b study, TMC114HIV3015, in six pregnant women showed lower mean exposure (AUC) of darunavir boosted with cobicistat during the second trimester (56% lower) and third trimester (50% lower), compared with 6 to 12 weeks postpartum. Mean darunavir C_{min} concentrations were around 90% lower during the second and third trimesters of pregnancy compared to postpartum. Compared to postpartum, exposure of cobicistat was 63% and 49% lower during the second and third trimesters of pregnancy, respectively.

Cobicistat boosted elvitegravir

Pharmacokinetic data from the IMPAACT P1026s study has shown that compared with paired postpartum data, plasma concentration after 24 hours of elvitegravir boosted with cobicistat was 81% lower in the second trimester and 89% lower in the third trimester. Plasma concentration after 24 hours of cobicistat was 60% and 76% lower in the second and third trimester, respectively.

Cobicistat boosted atazanavir

There are limited data from the use of atazanavir boosted with cobicistat in pregnant women. Plasma levels of cobicistat and consequently of atazanavir may decrease significantly during pregnancy.

Advice to Healthcare Professionals

- Therapy with darunavir/cobicistat or elvitegravir/cobicistat should not be initiated during pregnancy due to risk of virological failure and subsequent potential risk of mother-to-child transmission of HIV infection.
- Women who become pregnant during therapy with either of these treatment regimens should be switched to an alternative regimen.

Updates to product information

The product information for Prezista (darunavir), Rezolsta (darunavir and cobicistat) and Symtuza (darunavir, cobicistat, emtricitabine, tenofovir alafenamide) has been updated based on this information.

The product information for Genvoya (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide) and Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil) will be updated with this recommendation. The product information for Tybost (cobicistat) will be updated to reflect that darunavir/cobicistat should not be initiated during pregnancy and that plasma levels of cobicistat and consequently of atazanavir may decrease significantly during pregnancy.

Key Message

Pharmacokinetic data from clinical trials has shown exposures of darunavir boosted with cobicistat and elvitegravir boosted with cobicistat to be lower during the second and third trimesters of pregnancy compared to postpartum.

Therapy with darunavir/cobicistat or elvitegravir/cobicistat should not be initiated during pregnancy due to the potential risk of virological risk of failure. Virological failure increases the risk for mother-to-child transmission of HIV infection.

If a woman becomes pregnant while being treated with either of these regimens, she should be switched to an alternative regimen.

The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for all affected products are in the process of being updated with some products already updated.

Any suspected adverse reactions should be reported to the HPRA through the available options (www.hpra.ie).

* Products include Prezista, Rezolsta, Symtuza, Genvoya, Stribild and Tybost. Further details are available on www.hpra.ie and www.ema.europa.eu

Direct-Acting Antivirals for Chronic Hepatitis C – Risk of Hypoglycaemia in Patients with Diabetes

Direct-acting antiviral therapy*, used for the treatment of hepatitis C, has been associated with hypoglycaemia in patients with diabetes, particularly when treatment is initiated (1-7). Studies indicate that achieving sustained virological response (SVR) is associated with improvements in glycaemic control, compared to patients who relapse or are non-responders. Some studies reported the need to adjust patients' diabetic medication following changes in glucose metabolism, with up to 30% of patients requiring adjustments to their treatment, particularly within the first three months.

A review of the studies by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) confirmed the risk of hypoglycaemia in patient with diabetes who had been initiated on direct-acting antivirals for chronic hepatitis.

Advice to Healthcare Professionals

- Rapid reduction in hepatitis C viral load during initial treatment with direct-acting antiviral therapy for hepatitis C may lead to improvements in glucose metabolism in some patients with diabetes. This could potentially result in symptomatic hypoglycaemia if diabetic treatment is continued at the same dose.
- Diabetic patients commencing treatment with direct-acting antivirals should be advised of the risks of hypoglycaemia in association with treatment particularly during the first three months when the viral load is being reduced. Patients should be alert to potential changes in glucose tolerance, and diabetic medication or dosages should be modified as necessary.
- Healthcare professionals who initiate direct-acting antiviral therapy in diabetic patients should inform the healthcare professional in charge of the diabetic care of that patient.
- Patients with diabetes should be closely monitored for changes in blood glucose levels, particularly in the first three months of treatment.

Key Message

Diabetic patients initiated on direct-acting antiviral therapy for hepatitis C are at risk of hypoglycaemia, and should be monitored closely for changes in blood glucose levels, especially in the first three months of treatment.

Patients should be advised to monitor glucose levels closely because of the risk of hypoglycaemia. Diabetes medication or dosages should be modified where necessary.

Healthcare Professionals who initiate direct-acting antiviral therapy in diabetic patients should inform the healthcare professional in charge of the diabetic care of the patient.

Updates to product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) are currently underway to reflect this information.

Any suspected adverse reactions should be reported to the HPRA through the available options (www.hpra.ie).

* *Direct-acting antivirals daclatasvir (Daklinza), sofosbuvir/velpatasvir (Epclusa), ledipasvir/sofosbuvir (Harvoni), sofosbuvir (Sovaldi), sofosbuvir/velpatasvir/voxilaprevir (Vosevi), dasabuvir (Exviera), ombitasvir/paritaprevir/ritonavir (Viekirax), glecaprevir/pibrentasvir (Maviret) and elbasvir/grazoprevir (Zepatier). Further details are available on www.hpra.ie and www.ema.europa.eu*

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Biotin – Interference with clinical laboratory tests

Following a review by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC), it was considered that there was sufficient evidence to support a potential interference with clinical laboratory tests when patients are taking medicinal products for oral use containing ≥ 150 microgram biotin per dose unit and medicinal products for parenteral use containing ≥ 60 microgram biotin per dose unit.

Biotin is a water-soluble B vitamin that assists in the metabolism of fats, carbohydrates and protein. Biotin is not naturally occurring in the body so daily intake is necessary. Biotin is present in many authorised medicines and also in certain dietary supplements.

Test methods that apply the streptavidin-biotin interaction are commonly used in clinical practice for a variety of measurements including hormones, cardiac markers, tumour markers, infection markers and therapeutic drug monitoring. Biotin in blood or other samples, obtained from patients who are taking products that contain biotin, can interfere in such assays and cause clinically significant incorrect results. Depending on the test design, results may be falsely increased or falsely decreased and may lead to inappropriate patient management or misdiagnosis.

The risk of obtaining incorrect laboratory test results due to biotin is higher in the following patient groups:

- Patients with renal impairment, as they are more likely to have higher blood biotin concentrations and longer elimination times.
- Patients suffering from multiple sclerosis that are exposed to high doses of biotin (300mg per day) in clinical trials.
- Children with rare metabolic diseases (for example biotindase deficiency) as they are dependent on high doses of biotin.

Advice to Healthcare Professionals

Physicians

- Routinely ask patients about biotin use before ordering laboratory tests. If a patient is taking biotin, including medications containing biotin or supplements marketed for hair, skin and nail growth, consult the laboratory personnel before ordering the tests. Alternative tests may be available or a period of biotin withdrawal may be necessary to ensure accurate results.
- If results of laboratory tests do not match the clinical presentation and/or other investigations, the possibility of biotin interference should be taken into consideration.

Pharmacists

- Patients should be informed of the potential risk of interference with laboratory tests when receiving biotin-containing medicinal products.

Laboratory Personnel

- Be aware that specimens collected from patients taking biotin may yield incorrect test results
- Ensure that quality assurance practices are implemented in order to prevent and detect biotin interference, for example education and feedback on the risk of biotin interference when delivering test results obtained with susceptible tests to medical personnel; information on tests susceptible to interference and the impact of the interference on the test result, and the availability of alternative assays.
- Contact the test manufacturers in relation to any product specific questions, or if additional information on biotin interference is required.

Patients

- Patients should be advised that before undergoing any laboratory tests, they must tell their doctor or the laboratory personnel if they are taking or have recently taken biotin. If taking biotin for cosmetic purposes, use should be discontinued prior to laboratory testing. If taking biotin for therapeutic purposes, patients should not stop taking biotin without consulting their doctor.

The focus of this article is on laboratory tests, however there is also evidence in the literature of biotin interference in some Point of Care (near-patient) tests.

As laboratory tests which use biotin technology are classified as in vitro diagnostic medical devices (IVDs), the HPRA has also issued a [Safety Notice](#) highlighting this issue to relevant target groups.

Key Message

Biotin, that is present in certain medicinal products and dietary supplements, may interfere with laboratory tests that are based on a biotin/streptavidin interaction, leading to incorrect results.

The risk of interference is higher in renally impaired patients, patients suffering from multiple sclerosis taking high doses (300mg per day) and in children with rare metabolic diseases.

Physicians should routinely ask patients about biotin use before ordering laboratory tests. If a patient is taking medications containing biotin, or supplements marketed for hair, skin and nail growth, consult the laboratory personnel before ordering the tests. If results of laboratory tests do not match the clinical presentation and/or other investigations, the possibility of biotin interference should be taken into consideration.

Pharmacists should inform patients of the potential risk of interference with laboratory tests when receiving biotin-containing medicinal products.

Patients should be advised to inform healthcare professionals if they are taking biotin-containing medicines prior to any laboratory tests.

Laboratory personnel should be aware that specimens collected from patients taking biotin may yield incorrect test results. Quality assurance practices should be implemented in order to prevent and detect biotin interference.

Updates to product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for biotin-containing products are currently underway to reflect this information.

Any suspected adverse reactions suspected in association with biotin-containing medicines should be reported to the HPRA's pharmacovigilance system through the available options for reporting adverse reactions to human medicines, with any adverse incidents relating to the tests reported via the medical device incident forms, all of which are available under the logo 'report an issue' on the HPRA website (www.hpra.ie).

* Biotin-containing medicines include Ketovite, Pharmaton, Cernevit and Solvito. Further details are available on www.hpra.ie and www.ema.europa.eu

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

PRODUCT	SAFETY ISSUE
Lemtrada (alemtuzumab)	Restriction of use due to serious safety concerns
Quinolone and Fluoroquinolone antibiotics	Risk of disabling, long-lasting and potentially irreversible side effects and restrictions on use
Benlysta (Belimumab)	Increased risk of serious psychiatric events (depression, suicidal ideation or behavior, or self injury)
Genvoya, Stribild, Tybost	Increased risk of treatment failure and increased risk of mother-to-child transmission of HIV infection due to lower exposure of elvitegravir and cobicistat during the second and third trimesters of pregnancy
Xeljanz (tofacitinib)	Increased risk of pulmonary embolism and mortality in Rheumatoid arthritis patients receiving 10mg twice daily in clinical trials
SGLT2-Inhibitors	Risk of Fournier's gangrene
Carbimazole or Thiamazole	Strengthened advice on contraception and risk of acute pancreatitis

Correspondence/Comments should be sent to the Pharmacovigilance Section, Health Products Regulatory Authority, contact details below.