

In this Edition

- Methotrexate – New measures to avoid dosing errors
- SGLT2 inhibitors – Updated advice on monitoring ketone bodies in patients hospitalised for major surgical procedures or acute serious medical illnesses
- Ingenol mebutate (Picato▼) – Use with caution in patients with a history of skin cancer
- Fingolimod (Gilenya▼) – Contraindication in pregnant women and in women of child bearing potential not using effective contraception
- Levothyroxine – Close monitoring recommended in the event of a brand change
- Parenteral nutrition products for neonates and children below 2 years of age – Protect from light until administration is completed
- Direct Healthcare Professional Communications published on the HPRA website since the last Drug Safety Newsletter

Methotrexate – New measures to avoid dosing errors

Methotrexate* is authorised across the European Union for the treatment of both inflammatory diseases and cancers and is available in both oral and injectable formulations. When used in the treatment of inflammatory diseases, such as rheumatoid arthritis and psoriasis, methotrexate should be taken once a week. However, when used in the treatment of some cancers methotrexate may be taken more frequently. Errors in the prescribing or dispensing of methotrexate, as well as misunderstandings regarding the dosing schedule, have led to patients inadvertently taking the medicine daily instead of weekly for inflammatory diseases, with serious consequences, including fatality. The risk of medication error with methotrexate is well known and several measures are already in place to reduce the risk of such errors. However, despite these measures, a recently completed safety review at EU level indicated that medication errors continue to be reported at all stages of the medication process. Information regarding the risk of medication errors with methotrexate has previously been highlighted in the HPRA's Drug Safety Newsletter on a number of occasions, most recently in the [89th Edition](#).

The EU review undertaken by the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) examined the available evidence and, following consultation with patients and healthcare professionals, recommended additional measures to reduce the risk of medication errors with methotrexate. The measures include introduction of educational materials for oral methotrexate products for both patients and healthcare professionals, including a patient alert card, a recommendation to restrict prescribing of methotrexate-containing medicines and making warnings on the packaging of such medicines more prominent. In addition, methotrexate tablets will be provided in blister packs instead of bottles in order to help patients follow the once-weekly dosing. Please note that an implementation period for the introduction of blister packs for methotrexate tablets has been agreed with the companies responsible for the marketing of the products concerned. Thus, blister packs will not be immediately available for all methotrexate tablets.

Advice to Healthcare Professionals

- Only physicians with expertise in the use of methotrexate-containing medicines should prescribe them.
- Provide patients/carers with clear and complete dosing instructions on the once-weekly dosing regimen.
- Check carefully at every new prescription/dispensing that the patient/carer understands that the medicine must only be used once a week.
- Decide, together with the patient/carer, on which day of the week the patient is to use methotrexate.
- Inform the patient/carer of signs of overdose and instruct them to promptly seek medical advice in case of suspected overdose.

Key Message

Medication errors with serious consequences, including fatalities, have been reported when methotrexate intended for once-weekly use in inflammatory diseases was taken daily.

Healthcare professionals prescribing/dispensing methotrexate for inflammatory diseases should provide patients/carers with clear and complete dosing instructions and ensure that the patient/carer understands that the medicine is only to be taken once weekly.

The packaging and product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for methotrexate-containing products will be updated to make warnings regarding dosing errors more prominent and to reflect that the medicine is only to be prescribed by a doctor with expertise in the use of methotrexate.

Educational materials, including a patient alert card, will be developed by the companies responsible for the marketing of oral methotrexate products and will subsequently be provided to patients and healthcare professionals following approval by the HPRA.

Methotrexate tablets for weekly use will be provided in blister packs instead of bottles or tubes instead of bottles or tubes, when available.

A Direct Healthcare Professional Communication (DHPC) was circulated by the MAH, following approval by the HPRA, in November 2019.

All reports of suspected adverse reactions should be reported to the HPRA via the available methods (www.hpra.ie).

* Methotrexate-containing products include Jylamvo, Methofill, Methotrexate, Metoject and Nordimet. Further details are available on www.hpra.ie and www.ema.europa.eu.

SGLT2 inhibitors – Updated advice on monitoring ketone bodies in patients hospitalised for major surgical procedures or acute serious medical illnesses

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) has concluded its review of the risk of diabetic ketoacidosis (DKA) associated with sodium-glucose co-transporter 2 (SGLT2) inhibitors* in patients undergoing surgical procedures. SGLT2 inhibitors are indicated in adults for the treatment of Type 2 diabetes, as monotherapy or in combination with other diabetes medicines.

In 2016, following a review of the safety data available at the time, the PRAC considered that a small excess risk of DKA associated with SGLT2 inhibitors could not be excluded and that DKA with an atypical presentation may occur. The product information for SGLT2 inhibitors was updated thereafter to reflect this information and advise healthcare professionals that treatment with SGLT2 inhibitors should be interrupted in patients who are hospitalised for major surgery or acute serious illnesses due to the risk of DKA. This information was highlighted in the HPRA's Drug Safety Newsletter at that time ([75th edition](#)).

In early 2019, newly identified cases of DKA associated with SGLT2 inhibitors occurring in patients undergoing surgical procedures prompted further evaluation of the associated risk factors. Following an in-depth review of the available safety data, PRAC recommended that the Summary of Product Characteristics (SmPC) for SGLT2 inhibitors be updated to include a recommendation on how to assess for ketoacidosis in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. The updated warning recommends that ketones be monitored following interruption of SGLT2 inhibitor treatment in these patients. Treatment may be restarted when ketone values are normal and the patient's condition has stabilised. There is evidence that SGLT2 inhibitors may diminish the excretion of ketone bodies in the urine, thereby making urine measurement of ketone bodies less reliable compared to blood testing. Therefore, measurement of blood ketone levels is preferred to urine.

Advice to Healthcare Professionals

- In addition to the interruption of SGLT2 treatment in patients who are hospitalised for major surgical procedures or acute serious medical illnesses, ketone bodies should be monitored in these patients.
- Measurement of blood ketone levels is preferred to measurement of ketone bodies in the urine.
- Treatment may be restarted when the ketone values are normal and the patient's condition has stabilised.

Key Message

Cases of DKA have been reported in patients using SGLT2 inhibitors undergoing surgical procedures.

SGLT2 treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Ketone bodies should be monitored in these patients, preferably by measurement of blood ketone levels.

Treatment may be restarted when the ketone values are normal and the patient's condition has stabilised.

The Summary of Product Characteristics (SmPC) for SGLT2 inhibitors will be updated to include a recommendation on how to assess for ketoacidosis in patients who are hospitalised for major surgical procedures or acute serious medical illnesses.

All reports of suspected adverse reactions should be reported to the HPRA via the available methods (www.hpra.ie).

* SGLT2 inhibitor-containing products include Ebymect, Edistride, Forxiga, Qtern, Xigduo, Glyxambi, Jardiance, Synjardy, Segluromet, Steglatro, Steglujan, Invokana and Vokanamet. Further details are available on www.hpra.ie and www.ema.europa.eu.

Ingenol mebutate (Picato[▼]) – Use with caution in patients with a history of skin cancer

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) has commenced a review of data on skin cancer in patients using Picato[▼] (ingenol mebutate) and will assess the impact of the available data on the benefit-risk balance of Picato. This review was triggered by data from some clinical studies which indicated a higher number of skin cancer cases, including cases of squamous cell carcinoma in patients using ingenol mebutate or a related investigational medicinal product containing ingenol disoxate.

Picato* is indicated for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults and has been authorised for use throughout the European Union since 2012. Picato is available in two strengths, 0.015% and 0.05% ingenol mebutate.

In 2017, as a result of data from a randomised, doubleblind, vehicle-controlled study conducted with an investigational product of ingenol mebutate 0.06% in patients with actinic keratosis on trunk and extremities (study LP0105-1020), the product information for Picato was updated to reflect the potential for development of benign skin tumours (keratoacanthoma) in those treated with ingenol mebutate and this information was highlighted in the HPRA's Drug Safety Newsletter at that time ([79th edition](#)). In addition, an increased incidence of squamous cell carcinoma in those treated with ingenol mebutate compared to imiquimod was observed in the preliminary results of the ongoing randomised long-term safety study LP0041-63. A meta-analysis of four randomised, double-blind, vehicle-controlled studies of the related ester ingenol disoxate (a non-authorised treatment investigated for actinic keratosis) found an increased incidence of skin cancer at 14 months in those treated with ingenol disoxate. An imbalance in tumour incidence was noted for a number of tumour types including basal cell carcinoma, Bowen's disease and squamous cell carcinoma.

The product information for Picato has been updated to include a warning regarding reports of basal cell carcinoma, Bowen's disease and squamous cell carcinoma, and to advise that Picato should be used with caution in patients with a history of skin cancer.

Advice to Healthcare Professionals

- Picato should be used with caution in patients with a history of skin cancer.
- Continue to advise patients to be vigilant for any skin lesions developing within the treatment area and to seek medical advice immediately should any occur.

Key Message

Cases of squamous cell carcinoma have been reported in patients using ingenol mebutate and some clinical studies have indicated an increased incidence of skin cancer.

The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for Picato has been updated to include a warning regarding reports of basal cell carcinoma, Bowen's disease and squamous cell carcinoma, and to advise that Picato should be used with caution in patients with a history of skin cancer.

Patients should be advised to be vigilant for any skin lesions and to inform their doctor immediately should any occur.

A Direct Healthcare Professional Communication ([DHPC](#)) was circulated by the MAH, following approval by the HPRA, in September 2019.

All reports of suspected adverse reactions should be reported to the HPRA via the available methods (www.hpra.ie).

* Further details on Picato are available at www.hpra.ie and www.ema.europa.eu.

Fingolimod (Gilenya[▼]) – Contraindication in pregnant women and in women of child bearing potential not using effective contraception

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) recently concluded, following review of evidence submitted by the Marketing Authorisation Holder (MAH) for Gilenya^{▼*} (fingolimod), that fingolimod should be contraindicated in pregnant women and women of childbearing potential not using effective contraception.

Fingolimod is indicated as single disease modifying therapy in adults and paediatric patients aged 10 years and older, with highly active relapsing remitting multiple sclerosis (MS) despite a full and adequate course of treatment with at least one disease modifying therapy. Additionally, fingolimod is indicated in patients with rapidly evolving severe relapsing remitting MS defined by two or more disabling relapses in one year, and with one or more gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

The receptor affected by fingolimod (sphingosine-1-phosphate receptor) is involved in vascular formation during embryogenesis and animal studies conducted in rats have shown reproductive toxicity associated with fingolimod exposure.

Post-marketing data in humans suggest that use of fingolimod is associated with a two-fold increase in the risk of major congenital malformations when administered during pregnancy compared with the rate observed in the general population (2-3%; Eurocat¹).

The most frequently reported major malformations include:

- congenital heart disease such as atrial and ventricular septal defects, tetralogy of Fallot,
- renal abnormalities,
- musculoskeletal abnormalities.

Advice to Healthcare Professionals

For women of childbearing potential, ensure before treatment initiation and during treatment that:

- The patient is informed of the risk of harmful effects to the foetus associated with fingolimod treatment,
- A negative pregnancy test result is available before treatment initiation,
- Effective contraception is used during treatment and for 2 months after treatment discontinuation,
- Fingolimod treatment is stopped 2 months before planning a pregnancy.

If a woman becomes pregnant during treatment:

- Fingolimod must be discontinued,
- Medical advice should be given to the patient regarding the risk of harmful effects to the foetus,
- The pregnancy should be closely monitored and ultrasonography examinations should be performed.

Key Message

Post-marketing data suggest that use of fingolimod is associated with a two-fold increase in the risk of major congenital malformations when administered during pregnancy compared with the rate observed in the general population.

Fingolimod is now contraindicated in pregnant women and women of childbearing potential not using effective contraception.

A Direct Healthcare Professional Communication (DHPC) was circulated to relevant healthcare professionals in August 2019 and is available from the HPRA website (www.hpra.ie).

The product information for fingolimod (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) will be updated with the above information.

Educational materials for both patients and healthcare professionals will also be updated to facilitate patient counselling on the risk of reproductive toxicity with fingolimod.

All reports of suspected adverse reactions should be reported to the HPRA via the available options (www.hpra.ie).

* Further details on Gilenya[▼] are available on www.hpra.ie and www.ema.europa.eu.

Reference

1. European network of population-based registries for the epidemiological surveillance of congenital anomalies (www.eurocat-network.eu)

Levothyroxine – Close monitoring recommended in the event of a brand change

Until recently, Eltroxin was the only brand of levothyroxine authorised and marketed in Ireland. However, additional brands of levothyroxine-containing products have been authorised and are now available on the Irish market (see below).

Levothyroxine has a narrow therapeutic index. It is recommended that levothyroxine-containing products should not be used interchangeably, and should be prescribed and dispensed by brand name. Should a change to a different brand of levothyroxine-containing product become necessary, there is a need to closely monitor patients clinically and to perform thyroid function tests during the transition period due to a potential risk of thyroid imbalance. In some patients, a dose adjustment may be necessary. It is recommended that patients taking levothyroxine are advised of any changes in the brand prescribed or dispensed and therefore of the requirement for close monitoring and the need to consult their physician in the event of symptoms of thyroid imbalance. Patients changed from one formulation to another (i.e. tablets to oral solution) should also be advised of the change and monitored closely.

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) recently performed a routine assessment of safety and efficacy data relating to levothyroxine-containing products. Following this assessment, PRAC issued recommendations to update the product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) including advice for close monitoring of patients should a change in brand or formulation be necessary.

Advice to Healthcare Professionals

- Levothyroxine-containing products should not be used interchangeably, and should be prescribed and dispensed by brand name.
- Patients on established levothyroxine treatment who are changed to a different brand or pharmaceutical form (i.e. tablets to oral solution) should be closely monitored clinically and have thyroid function tests performed during the transition period due to a potential risk of thyroid imbalance. In some patients, a dose adjustment may be necessary.
- Patients should be informed of any changes in the brand of levothyroxine prescribed or dispensed and therefore of the requirement for close monitoring should a change become necessary.
- Patients should be made aware of the symptoms of thyroid imbalance and should be encouraged to consult their physician in the event that they experience any of these symptoms.

Key Message

Levothyroxine-containing products should be prescribed and dispensed by brand name. Should a change to a different brand or pharmaceutical form of levothyroxine-containing product become necessary for a patient, there is a need to undertake close clinical and laboratory monitoring of thyroid function during the transition period due to a potential risk of thyroid imbalance. In some patients, a dose adjustment may be necessary.

The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for levothyroxine-containing products will be updated to include a warning regarding the need to monitor patients who are switching from one levothyroxine product to another.

All reports of suspected adverse reactions should be reported to the HPRA via the available methods (www.hpra.ie).

* *Levothyroxine-containing products include Eltroxin, Levothyroxine Teva, Oroxine and other generic levothyroxine products. Further details are available on www.hpra.ie.*

Parenteral nutrition products for neonates and children below 2 years of age – Protect from light until administration is completed

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) recently completed a review of data relating to adverse outcomes in neonates that were treated with parenteral nutrition (PN) products* not protected from light. PN products are indicated for use in pre-term and term neonates when oral or enteral nutrition is not possible, insufficient or contraindicated.

Laboratory and clinical studies have shown that exposure of PN products to light causes the formation of peroxides and other degradation products that are quantifiable in experimental PN solutions, in animals, and in neonates. PN products containing vitamins and/or lipids may be most susceptible. Ambient and environmental light and especially phototherapy contribute to generation of peroxides.

Data in support of this effect from light exposure include studies showing that the formation of PN photodegradation products can be slowed down or prevented by the application of various light protection measures. A meta-analysis of four randomised controlled trials suggests a reduced mortality at 36 weeks gestational age when light protection is in place (Chessex *et al*, 2017).

The clinical relevance of light protection of PN products is especially notable in premature infants with high nutritional requirements and slow intravenous infusion rates. Several conditions related to prematurity with insufficient anti-oxidative capacity are thought to be risk factors for the underlying pathological mechanism related to generation of peroxides. Very premature neonates are considered at high risk of oxidative stress related to multiple risk factors including oxygen therapy, weak immune system and inflammatory response with reduced oxidant defence and exposure to high energy light (phototherapy). While data on harm primarily concerns premature neonates, light protection should be provided for such products also administered to neonates and children below 2 years of age, as a precautionary measure.

Light protection of PN products is recommended in paediatric PN guidelines by the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), including coverage of both the container and administration sets.

The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for the PN products concerned will be updated to reflect the need to protect these products from exposure to light.

Advice to Healthcare Professionals

- When PN products containing amino acids and/or lipids are used in neonates and children below 2 years of age, the solution (containers and administration sets) should be protected from light exposure until administration is completed.

Key Message

During administration to neonates and children below 2 years of age, parenteral nutrition (PN) products containing amino acids and/or lipids, should be protected from light (containers and administration sets).

Use of light-exposed PN products containing amino acids and/or lipids, particularly in admixtures with vitamins and/or trace elements, may have adverse effects on clinical outcome in neonates. This is because exposure of such solutions to light causes formation of peroxides and other degradation products.

Premature neonates are considered at high risk of oxidative stress related to multiple risk factors including oxygen therapy, phototherapy, weak immune system and inflammatory response with reduced oxidant defence.

The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for the PN products concerned will be updated to reflect the need to protect them from exposure to light.

A Direct Healthcare Professional Communication ([DHPC](#)) was circulated by the MAHs, following approval by the HPRA, in September 2019.

All reports of suspected adverse reactions should be reported to the HPRA via the available methods (www.hpra.ie).

* Affected parenteral nutrition products include Clinimix, Intralipid, Numeta G13%E, Numeta G16%E, Primene, SMOFlipid and Vaminolact. Further details are available on www.hpra.ie.

Reference

1. Chessex P, Laborie S, Nasef N, Masse B, Lavoie JC. Shielding Parenteral Nutrition From Light Improves Survival Rate in Premature Infants. *JPEN J Parenter Enteral Nutr.* 2017;41(3):378-383

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

PRODUCT	SAFETY ISSUE
Gilenya (fingolimod)	New contraindication in pregnant women and in women of childbearing potential not using effective contraception
BLINCYTO (blinatumomab)	Clarification of premedication with dexamethasone in paediatric patients
Lucentis (ranibizumab) 10 mg/mL pre-filled syringe	Plunger on syringe too stiff
Picato (ingenol mebutate)	Use with caution in patients with a history of skin cancer
Parenteral nutrition products	Light protection required to reduce the risk of serious adverse effects in premature neonates
Mitomycin-C Kyowa 40 mg	Restricted to intravesical administration only for treatment of superficial bladder cancer
Lucentis (ranibizumab) 10 mg/mL pre-filled syringe	Update – Plunger on syringe too stiff
Methotrexate	Recommendations to avoid potentially fatal dosing errors when using methotrexate for inflammatory diseases
Baxter Electrolyte Solutions for Infusion, with and without Glucose	Update to Product Information – Risk of Hyponatraemia