Erythromycin – Updated warnings regarding cardiovascular risks and infantile hypertrophic pyloric stenosis

Erythromycin* is a macrolide antibiotic and as such is known to be associated with a risk of QT-prolongation and cardiac arrhythmia, as reflected in the approved product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for these medicinal products. As part of a recent routine periodic assessment of erythromycin-containing medicines, the European Medicines Agency’s (EMA’s) Pharmacovigilance Risk Assessment Committee (PRAC) considered data from observational studies that identified a rare, short-term risk of cardiovascular events associated with macrolides, including erythromycin.\(^1,2,3\) These cardiovascular events include arrhythmia, myocardial infarction and cardiovascular mortality. Based on the available data, the PRAC recommended that consideration of cardiovascular risks should be balanced with known treatment benefits when prescribing erythromycin-containing medicines, particularly in patients at high risk of cardiovascular events. Erythromycin should not be given to patients with a history of QT prolongation or ventricular cardiac arrhythmia, nor should it be given to patients with electrolyte disturbances. Similar recommendations were previously introduced for clarithromycin-containing medicines, as highlighted in the 88th Edition of the HPRA’s Drug Safety Newsletter.

As part of the PRAC’s assessment, an extensive literature review was undertaken and it was considered that there was consistent evidence across a reasonable body of literature to support an association between exposure to erythromycin in infants and the risk of infantile hypertrophic pyloric stenosis (IHPS). Data from three meta-analyses suggested that erythromycin exposure was associated with a two- to three-fold increase in the risk of IHPS in children less than 6 months of age, particularly in those exposed during the first 14 days of life.\(^4,5,6\) The available data suggest a risk of 2.6% following exposure to erythromycin during this time period, while the risk of IHPS in the general population is estimated to be 0.1-0.2%.

The product information for erythromycin-containing medicines that are systemically absorbed has been updated to reflect current knowledge regarding the risks associated with treatment, as described above, while details of a recently identified increased risk of bleeding associated with concomitant use of the direct acting oral anticoagulant, rivaroxaban, has also been included.

Advice to Healthcare Professionals

- Erythromycin should not be given to patients with a history of QT prolongation or ventricular cardiac arrhythmia, nor should it be given to patients with electrolyte disturbances.
- Consideration of the cardiovascular risks associated with macrolide antibiotics should be balanced with known treatment benefits when prescribing erythromycin-containing medicines.
- The product information for erythromycin-containing medicines that are systemically absorbed has been updated to reflect current knowledge regarding the risks associated with treatment, including cardiovascular risk, risk of IHPS, and bleeding risk in association with concomitant rivaroxaban treatment.

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Key messages

Observational studies have identified a rare, short-term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolide antibiotics, including erythromycin. Consideration of these findings should be balanced with treatment benefits when prescribing erythromycin in patients at high risk of cardiovascular events.

There is evidence of an increased risk of bleeding when erythromycin is used concomitantly with the direct acting oral anticoagulant, rivaroxaban.

Epidemiological studies including data from meta-analyses suggest a two- to three-fold increase in the risk of infantile hypertrophic pyloric stenosis (IHPS) following exposure to erythromycin in infancy.

Suspected adverse reactions should be reported to the HPRA via the available methods ([www.hpra.ie/report](http://www.hpra.ie/report)).

References

Vascular Endothelial Growth Factor (VEGF) pathway inhibitors – Risk of aneurysm and artery dissection

Angiogenesis is a complex process by which new blood vessels are formed from the endothelium of a pre-existing vasculature. This process plays a role in both physiological and pathological conditions. Vascular Endothelial Growth Factor (VEGF) and its receptors have a central role in tumour angiogenesis and tumour growth, and it is thought that VEGF pathway inhibitors* exert an effect through blockage of the signal transduction pathways. However, given the crucial physiological role of VEGF in vascular protection and vascular homeostasis, inhibition of VEGF activity may compromise these protective and homeostatic mechanisms and affect the integrity of the vascular matrix.

The European Medicines Agency’s (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has completed a review of VEGF pathway inhibitors with respect to the potential risk of aneurysm and artery dissection. Prior to this review, the product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for a number of VEGF pathway inhibitors already included warnings regarding the risk of aneurysm and/or artery dissection. Similarly, the product information for VEGF pathway inhibitors for systemic administration already described the risk of hypertension, which is an important predisposing factor for artery dissection and aneurysm. Having considered reports of aneurysm and artery dissection in the EMA’s adverse reaction database (EudraVigilance), some of which were fatal, as well as the totality of available evidence, the product information for all VEGF pathway inhibitors for systemic administration have recently been updated to reflect this risk. However, the review concluded that based on the available evidence, a causal association could not be established between these risks and the two VEGF pathway inhibitors that are authorised for use in ocular conditions and administered by intravitreal injection, ranibizumab (Lucentis) and aflibercept (Eylea).

Advice to Healthcare Professionals

• The use of VEGF pathway inhibitors for systemic administration in patients with or without hypertension may promote the formation of aneurysm and/or artery dissection, which may be fatal in some cases.
• Before initiating treatment, this risk should be carefully considered in patients with additional risk factors such as hypertension or history of aneurysm.
• Any modifiable risk factors such as hypertension should be reduced as far as possible in patients treated with VEGF pathway inhibitors for systemic administration.
• Monitor and treat patients for hypertension in accordance with recommendations in the Summary of Product Characteristics (SmPC) for the relevant VEGF pathway inhibitors for systemic administration.
• The product information for VEGF pathway inhibitors for systemic administration has recently been updated to provide further information on the risk of aneurysm and artery dissection.
Implanon NXT* is a non-biodegradable, single-rod, long-acting, etonogestrel-containing hormonal contraceptive implant, which is inserted subdermally. There have been reports of migration of the implant within the arm from the insertion site, which may be related to deep insertion or external forces (e.g. manipulation of the implant or contact sports). There also have been rare post-marketing reports of implants located within the vessels of the arm and the pulmonary artery, which may be related to deep insertions or intravascular insertion. Existing warnings and recommendations for insertion (site and position of the arm during insertion) and removal of Implanon NXT implant have recently been updated to further minimise the risk of neurovascular injury and implant migration, based on the advice of relevant experts. A Direct Healthcare Professional Communication (DHPC), with full details of the changes, was recently circulated to healthcare professionals (HCPs) by the marketing authorisation holder (MAH i.e. the company which holds the licence for a product), and is available on the HPRA website. A summary of key aspects is provided below.

### Advice to Healthcare Professionals

- **Updated position of the arm:** The woman’s arm should be flexed at the elbow with her hand underneath her head (or as close as possible) during insertion and removal of the implant.

- **Updated implant insertion site:** The implant should be inserted subdermally just under the skin at the inner side of the non-dominant upper arm. The updated insertion site is overlying the triceps muscle about 8-10 cm from the medial epicondyle of the humerus and 3-5 cm posterior to the sulcus (groove) between the biceps and triceps muscles.

- The correct location of the implant (subdermally) should be confirmed by palpation by both the HCP and the woman at the time of insertion. Deeply-placed implants should be localised and removed as soon as possible to avoid the potential for distant migration.

- Ensure women are supplied with a Patient Alert Card** and instructed to show the card to the HCP at any visits related to the use of the implant.

- Palpate the implant at each check-up visit and instruct the woman to contact her doctor as soon as possible if she cannot feel the implant at any time between check-ups.

- In the case of an implant that is not palpable, consult the Patient Alert Card or medical record to verify the arm which contains the implant. If the implant cannot be palpated, it may be deeply located or have migrated. Consider that it may lie close to vessels and nerves. Non-palpable implants should only be removed by a HCP experienced in removing deeply placed implants and who is familiar with localising the implant and the anatomy of the arm.

- Videos demonstrating the insertion and removal of Implanon NXT are available at www.implanonnxtvideos.eu.

- The Product Information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) and Patient Alert Card for Implanon NXT have been updated accordingly, and should be consulted for detailed usage instructions.

- It remains a strong recommendation that Implanon NXT be inserted and removed only by healthcare professionals (HCPs) who have completed training in the use of the Implanon NXT applicator and the techniques for insertion and removal of the implant, and, where appropriate, that supervision be requested prior to inserting or removing the implant.

- Similarly, the recommendation that the woman returns for a medical check-up 3 months after insertion of the implant remains unchanged.

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* VEGF-inhibitor medicinal products reviewed include aflibercept (Zaltrap and Eylea), axitinib (Inlyta), bevacizumab (Avastin and Mvasi), cabozantinib (Cabometyx and Cometriq), lenvatinib (Kisplyx and Lenvima), nintedanib (Ofev and Vargatef), ponatinib (Iclusig), pazopanib (Votrient), pegaptanib (Macugen); ranibizumab (Lucentis), ramucirumab (Cyramza), regorafenib (Stivarga), sunitinib (Sutent), sorafenib (Nexavar), tivozanib (Fotivda), and vandetanib (Caprelsa). Further details are available at www.ema.europa.eu.

1. The Marketing authorisation for pegaptanib (Macugen) has been withdrawn since this review.
Key messages

Cases of neurovascular injury and migration of the Implanon NXT implant from the insertion site within the arm, or in rare cases into the pulmonary artery, have been reported.

To further minimise the risk of neurovascular injury and implant migration, the instructions for insertion and removal of the implant have been updated. Further information can be found on the HPRA website in a Direct Healthcare Professional Communication or in the updated product information.

It is strongly recommended that Implanon NXT be inserted and removed only by HCPs who have completed training in the use of the Implanon NXT applicator and the techniques for insertion and removal of the implant. Non-palpable implants should only be removed by a HCP experienced in removing deeply placed implants and who is familiar with localising the implant and the anatomy of the arm.

Videos demonstrating the insertion and removal of Implanon NXT are available at www.implanonnxtvideos.eu.

Ensure women are supplied with a Patient Alert Card and instructed to show the card to the HCP at any visits related to the use of the implant.

Suspected adverse reactions should be reported to the HPRA via the available methods (www.hpra.ie/report).

* Further details on Implanon NXT are available at www.hpra.ie.

** The Implanon NXT package contains a Patient Alert Card intended for the woman, which records the batch number of the implant. HCPs are requested to record the date of insertion, the arm of insertion and the intended date of removal on the Patient Alert Card. Patients should be instructed to keep the Patient Alert Card in a safe place and show the card at any visits related to the use of her implant. The Patient Alert Card also contains instructions for the patient to occasionally gently palpate the implant to be sure that she knows its location. Patients should be instructed to contact their doctor as soon as possible if at any time they cannot feel the implant. The package also includes adhesive labels intended for HCP records showing the batch number. This information should be included in the electronic medical records of the patient if such are used.

Insulin-containing medicines – Risk of cutaneous amyloidosis and potential for associated changes in glycaemic control

The European Medicines Agency’s Pharmacovigilance Risk Assessment Committee (PRAC) recently completed a review of the risk of injection site cutaneous amyloidosis associated with insulin-containing medicines. The review considered reports of cutaneous amyloidosis from the published literature and the European database of suspected adverse reactions (EudraVigilance). A number of spontaneous reports involving cutaneous amyloidosis described changes in glycaemic control, with subsequent recovery of glycaemic control reported following injection site rotation and implementation of correct injection technique.

Having considered the available data, the PRAC concluded that the cumulative evidence supports a causal relationship between insulin-containing medicines and cutaneous amyloidosis, with the potential for associated changes in glycaemic control. Based on the available evidence, the risk of cutaneous amyloidosis associated with insulin-containing medicines is considered to be a class effect.

Lipodystrophy is already a known side effect associated with insulin-containing medicines and the product information for these medicines contain a recommendation to rotate injection site to reduce the risk of lipohypertrophy. The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for insulin-containing medicines will now be updated to reflect the risk of cutaneous amyloidosis and to further highlight the need for injection site rotation.

Advice to Healthcare Professionals

- Injection site cutaneous amyloidosis has been reported in association with use of insulin-containing medicinal products.
- Patients should be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis.
- There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites of lipodystrophy or cutaneous amyloidosis.
- Blood glucose monitoring is recommended after a change in the injection site to an unaffected area, as sudden changes have been reported to result in hypoglycaemia.
- Dose adjustment of antidiabetic medications may need to be considered following a change in the injection site to an unaffected area.
**Key messages**

Patients should be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and injection site cutaneous amyloidosis.

Blood glucose monitoring is recommended after a change in the injection site to an unaffected area, as sudden changes have been reported to result in hypoglycaemia. Dose adjustment of antidiabetic medications may also need to be considered.

The product information for insulin-containing medicines will be updated to reflect current knowledge on the risk of cutaneous amyloidosis associated with injection.

Suspected adverse reactions should be reported to the HPRA via the available methods ([www.hpra.ie/report](http://www.hpra.ie/report)).

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**Leuprorelin-containing depot medicines – Risk of lack of efficacy due to incorrect reconstitution and administration**

Leuprorelin is a gonadotropin releasing hormone agonist used in the treatment of prostate cancer, breast cancer, conditions that affect the female reproductive system (endometriosis, symptomatic uterus myomatous, uterine fibrosis) and early puberty. A risk of lack of efficacy due to incorrect reconstitution and administration of Eligard, a leuprorelin-containing depot medicine, was previously identified and reviewed by the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC). Details of the review undertaken at that time were highlighted in the [66th edition](http://www.hpra.ie) of the HPRA's Drug Safety Newsletter.

Despite implementation of risk minimisation measures following the previous review, cases of handling errors potentially resulting in lack of efficacy continued to be reported in association with leuprorelin-containing depot medicines, which led to a further review of the issue, which was recently completed. The PRAC noted that the presentations, as well as the preparation, reconstitution and administration process vary across the different leuprorelin-containing medicinal products. It was concluded that the risk of handling errors is increased when there are multiple steps in the product reconstitution and administration process. The PRAC recommended that further measures be taken to minimise the risk of handling errors, including updates to the product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) to emphasise the need to strictly follow the instructions for reconstitution and administration. It was also recommended that these products should only be prepared and administered by healthcare professionals who are familiar with the relevant reconstitution and administration procedures. If suspected or known handling errors with leuprorelin-containing depot medicines occur, patients should be monitored appropriately. Additionally, the company that markets Eligard has been requested to modify the device to reduce the number of steps involved in the preparation process.

**Advice to Healthcare Professionals**

- Leuprorelin-containing depot medicines should be prepared, reconstituted and administered only by healthcare professionals who are familiar with these procedures.
- It is important to strictly follow instructions for reconstitution and administration provided in the product information.
- If suspected or known handling errors with leuprorelin-containing depot medicines occur, patients should be monitored appropriately.

**Key messages**

Handling errors have been reported with leuprorelin-containing depot medicinal products, potentially resulting in lack of efficacy. The risk of handling errors is increased when there are multiple steps in the product reconstitution and administration process.

Leuprorelin-containing depot medicines should be prepared, reconstituted and administered only by healthcare professionals who are familiar with these procedures.

It is important to strictly follow instructions for reconstitution and administration provided in the product information.

The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for leuprorelin-containing depot medicines will be updated to emphasise the need to strictly follow the instructions for reconstitution and administration.

A Direct Healthcare Professional Communication (DHPHC) was circulated by the Marketing Authorisation Holders (MAHs), following approval by the HPRA, in July 2020.

Suspected adverse reactions, including those associated with medication errors, should be reported to the HPRA via the available methods ([www.hpra.ie/report](http://www.hpra.ie/report)).

*Leuprorelin-containing depot medicines licensed in Ireland include Eligard, Leuprex, Lutrate and Prostap. Further details on leuprorelin-containing depot medicines are available at [www.hpra.ie](http://www.hpra.ie).*
Xeljanz® (tofacitinib) – Updated recommendations due to increased risk of venous thromboembolism and serious and fatal infections

Xeljanz® (tofacitinib) is indicated for the treatment of rheumatoid arthritis and psoriatic arthritis at a recommended dose of 5 mg twice daily. Xeljanz® is also approved for treatment of ulcerative colitis at a recommended dose of 10 mg twice daily for induction for 8 weeks and thereafter at a dose of 5 mg twice daily for maintenance. The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) conducted a review of the risk of venous thromboembolism (VTE) and all-cause mortality in patients treated with tofacitinib and in May 2019, following the preliminary analysis of data from an ongoing clinical trial (study A3921133), recommended that the 10 mg twice daily dose of tofacitinib should be contraindicated in patients at high risk of pulmonary embolism (PE) as a temporary measure. Commencement of the review and recommendations made at that time were highlighted in the 93rd edition of the HPRA's Drug Safety Newsletter.

The PRAC review has now concluded and the temporary measures outlined above have been updated with revised recommendations to minimise the risks of VTE and serious infections associated with use of Xeljanz® based on the interim analyses of study A3921133. The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) and educational materials for Xeljanz® have been updated accordingly.

Study A3921133 is an ongoing open-label clinical trial (n = 4,362) evaluating the cardiovascular safety of tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily, compared with a tumour necrosis factor (TNF) inhibitor therapy in patients with rheumatoid arthritis who are 50 years of age or older and have at least one cardiovascular risk factor. An analysis of interim results identified a dose-dependent increased risk of VTE (PE and deep vein thrombosis (DVT)) in patients treated with tofacitinib compared to TNF inhibitors. In a subgroup analysis in patients with VTE risk factors, the risk for PE was further increased. In an ongoing extension trial evaluating the safety of tofacitinib in the treatment of ulcerative colitis (UC), cases of PE and DVT have also been observed in patients with underlying VTE risk factors using tofacitinib 10 mg twice daily. In the interim analysis of study A3921133, increased mortality within 28 days of last treatment was observed in patients treated with tofacitinib compared to TNF inhibitors. Mortality was mainly due to cardiovascular events, infections and malignancies. The risk of serious infections and fatal infections was further increased in elderly patients above 65 years of age compared to younger patients.

Advice to Healthcare Professionals

- Tofacitinib should be used with caution in patients with known risk factors for VTE, regardless of indication and dosage.
- Use of tofacitinib 10 mg twice daily for maintenance treatment in patients with UC who have known VTE risk factors is not recommended, unless there is no suitable alternative treatment available.
- For treatment of rheumatoid arthritis and psoriatic arthritis, the recommended dose of 5 mg twice daily should not be exceeded.
- Patients should be informed of the signs and symptoms of VTE before they start tofacitinib therapy and advised to seek prompt medical help if they develop these symptoms during treatment.
- Patients over 65 years of age are at further increased risk of serious infections and mortality due to infections. Therefore, tofacitinib should only be considered in these patients if no suitable alternative treatment is available.

Key messages

A dose-dependent increased risk of serious venous thromboembolism (VTE), including cases of pulmonary embolism, some of which were fatal, and deep vein thrombosis has been observed in patients taking tofacitinib.

Tofacitinib should be used with caution in patients with known risk factors for VTE, regardless of indication and dosage. Use of tofacitinib 10 mg twice daily for maintenance treatment in patients with ulcerative colitis who have known VTE risk factors is not recommended, unless there is no suitable alternative treatment available.

For treatment of rheumatoid arthritis and psoriatic arthritis, the recommended dose of 5 mg twice daily should not be exceeded. Patients should be informed of the signs and symptoms of VTE before they start tofacitinib therapy and advised to seek prompt medical help if they develop these symptoms during treatment.

Patients over 65 years of age are at further increased risk of serious infections and mortality due to infections. Therefore, tofacitinib should only be considered in these patients if no suitable alternative treatment is available.

The product information and educational materials for Xeljanz® have been updated to reflect the outcome of the PRAC review. A Direct Healthcare Professional Communication (DHPC) was circulated by the Marketing Authorisation Holder (MAH) for Xeljanz®, following approval by the HPRA, in February 2020.

▼ This medicinal product is subject to additional monitoring and as such, all suspected adverse reactions associated with its use should be reported to the HPRA via the available methods (www.hpra.ie/report). Further information on the additional monitoring of medicines is available at www.hpra.ie.

Risk of respiratory depression and sedation associated with Epaclob 1mg/ml and 2mg/ml oral suspension (clobazam)

Epaclob 1mg/ml and 2mg/ml oral suspensions are not bioequivalent to clobazam tablets and particular care should be taken when prescribing these medications. When taking Epaclob oral suspension, clobazam reaches higher plasma levels than the same dose in a tablet formulation. This may lead to an increased risk of respiratory depression and sedation, which may be most noticeable when switching to Epaclob oral suspension from tablet formulations of clobazam. Please see the Direct Healthcare Professional Communication (DHPC) distributed by the Marketing Authorisation Holder (MAH) in July 2020 for further information.

Access to current versions of Product Information

Healthcare professionals are reminded that SmPCs for all products currently authorised in Ireland are accessible on the HPRA website (www.hpra.ie). The HPRA advises healthcare professionals not to retain printed versions of Summary of Product Characteristics (SmPC) documents. As these documents are subject to frequent content updates, including changes to safety and dose related information, we recommend that you visit our website as necessary to access the most up-to-date versions.

Register for alerts from the HPRA website

Healthcare professionals are encouraged to register here to receive HPRA alerts when important new safety information and updated recommendations become available, including links to the DSN, updated prescribing recommendations arising from EU reviews, and Direct Healthcare Professional Communications (DHPCs). The HPRA website also provides on-line access to the latest approved product information for medicines (Summary of Product Characteristics and Package Leaflet) and to educational materials such as prescriber guides, patient guides and administration guides, which are aimed at minimising important risks and maximising benefits of specific medicinal products.

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

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