

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) 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.

Key Message

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

* Systemically absorbed erythromycin-containing medicines licensed in Ireland include Erythrocin, Erythroped, and Primacine. Further details on erythromycin-containing medicines are available at www.hpra.ie.

References

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- 6) Almaramhy HH, Al-Zalabani AH. The association of prenatal and postnatal macrolide exposure with subsequent development of infantile hypertrophic pyloric stenosis: a systematic review and meta-analysis. *Ital J Pediatr.* 2019 Feb 4;45(1)20.

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