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Direct Healthcare Professional Communication on ondansetron (Zofran and generics) and dose-dependent QT interval prolongation – new dose restriction for intravenous (IV) use

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DEAR HEALTHCARE PROFESSIONAL,

SUMMARY

- A single dose of intravenous ondansetron given for the prevention of chemotherapy-induced nausea and vomiting (CINV) in adults, **must not exceed 16 mg** (infused over at least 15 minutes).

- Ondansetron causes a dose-dependent prolongation of the electrocardiographic-corrected QT interval (QTc), which can lead to Torsade de Pointes, a potentially life-threatening heart arrhythmia. Because of this potential safety risk, there are new dose restrictions in place for use of IV ondansetron.

- Ondansetron should be avoided in patients with congenital long QT syndrome.

- Caution must be used if administering ondansetron to patients with risk factors for QT interval prolongation or cardiac arrhythmias. These include electrolyte abnormalities, congestive heart failure, bradyarrhythmias or use of other medicines that lead to electrolyte abnormalities,. Hypokalemia and hypomagnesaemia should be corrected prior to ondansetron administration.

- Caution should be exercised when ondansetron is coadministered with medicinal products, including some cytotoxic agents that prolong the QT interval**.**

- There are no changes to the recommended oral and rectal dosing for CINV in adult patients.

- There are no changes to the recommended IV or oral dosing for the prevention and treatment of post-operative nausea and vomiting (PONV) in adult patients.

- There are no changes in the recommended IV or oral dosing for any indication in the paediatric population.

The information in this communication has been agreed with the Irish Medicines Board.

Further information on the safety concern

The risk of prolongation of QTc interval and cardiac arrhythmia, including Torsade de Pointes, with ondansetron use were already included in the product information. However, the precise degree of QTc prolongation for ondansetron had not been previously established.

Results from a recently completed study demonstrate that ondansetron causes a dose-dependent prolongation of the QTc. The study was a blinded, randomized, placebo- and active-controlled (moxifloxacin) crossover study in 58 healthy adult men and women. Ondansetron doses were 8 mg and 32 mg infused intravenously (IV) over 15 min.

At 32 mg IV over 15 min, the maximum mean QTc interval prolongation was approximately 20 ms. This degree of prolongation suggests that this dose may result in a clinically significant degree of QT prolongation in certain individuals. At 8 mg IV over 15 min, the maximum mean QTc

prolongation was approximately 6 ms, which is generally considered to be associated with less risk of proarrhythmia.
In this study, there were no QTc measurements greater than 480 ms and there were no increases in QTc greater than 60 ms. No significant changes were seen in the measured electrocardiographic PR or QRS intervals.

Extrapolating from the observations from this study, it is possible to predict that an IV dose of 16 mg over 15 minutes would cause a QTc prolongation of 9.1 (95% confidence interval 11.2) ms. For the oral and rectal formulations, the various dosages are predicted to have less than 10 ms effect on QTc prolongation.

Despite the differences in the degree of QT prolongation between the doses tested in this study, there have been post-marketing reports of QT prolongation and TdP in patients using ondansetron at both low and high doses.
The results of the study have lead to new recommendations that a single dose of intravenous ondansetron given for the prevention of CINV in adults must not exceed 16 mg IV (infused over at least 15 minutes).
This letter is not a comprehensive presentation of the risk profile of ondansetron. Please see the prescribing information in the Annex for updated information on the risk of QTc prolongation, and additional safety information.

FURTHER ADVICE FOR HEALTHCARE PROFESSIONALS

Please share the information in this letter with relevant colleagues and health care personnel. Please also report suspected adverse reactions with any medicine or vaccine to the Irish Medicines Board through on http://www.imb.ie/EN/Safety--Quality/Online-Forms/Human-Medicine-Adverse-Drug-Reaction.aspx or call (01) 676 4971.

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset and treatment dates.

- Any suspected adverse reactions with ondansetron (Zofran) may also be reported to GlaxoSmithKline by contacting 1800 244 255 or e-mail Ireland.drugsurveillance@gsk.com.

FURTHER INFORMATION

If you have any questions about the new information for Zofran, please contact GlaxoSmithKline on 1800 244 255 or e-mail ukmedinfo@gsk.com.

Yours Sincerely,

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Annex: Revised wording for Zofran Summary of Product Characteristics (SPC) and Patient information Leaflet (PIL)