NATIONAL PBM BULLETIN

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**DEPARTMENT OF VETERANS AFFAIRS VETERANS HEALTH ADMINISTRATION (VHA)
PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP),
AND CENTER FOR MEDICATION SAFETY (VA MEDSAFE)**

ONDANSETRON HYDROCHLORIDE (ZOFRAN®) AND VOLUNTARY MARKET WITHDRAWAL OF THE 32 MG SINGLE INTRAVENOUS (IV) DOSE DUE TO CARDIAC RISKS

I. ISSUE [1]

According to the FDA, the 32 mg, single, intravenous (IV) dose of the anti-nausea drug ondansetron hydrochloride (Zofran®) is being withdrawn from the market due to potentially fatal cardiac risks associated with QT prolongation. Products affected include:

Generic name	Sponsor	Application Number
Ondansetron Hydrochloride Injection, USP premix in Intravia Plastic Container	Baxter Healthcare Corporation	NDA 021915
Ondansetron Hydrochloride and Dextrose in Plastic Container	Hospira	ANDA 077348
Ondansetron Hydrochloride and Dextrose in Plastic Container	Teva	ANDA 077480
Ondansetron Hydrochloride and Dextrose in Plastic Container	Bedford Labs	ANDA 078291
Ondansetron Hydrochloride and Dextrose in Plastic Container	Claris Lifesciences	ANDA 078308

II. BACKGROUND [3]

Ondansetron hydrochloride (Zofran®), a 5HT-3 receptor antagonist, prevents nausea and vomiting induced by chemotherapy, radiation, and surgery. Dosage forms include an injection for IV use (2 mg/mL) as well oral products (4 mg and 8 mg tablets, 4 mg and 8 mg orally disintegrating tablets, and a 4 mg/5 mL oral solution). [3]

III. DISCUSSION [1, 2]

As part of their ongoing safety review, FDA required GlaxoSmithKline to conduct a thorough QT study in order to determine the severity of QT interval prolongation associated with the use of ondansetron hydrochloride (Zofran®). Preliminary review of these study results showed dose-dependent QT-prolongation with ondansetron hydrochloride (Zofran®), and specifically with the 32mg single IV dose (maximum mean difference in QTcF from placebo after baseline-correction was 20 msec compared to 6 msec with a single IV dose of 8 mg). This led to the removal of the 32 mg single IV ondansetron dose from the product label earlier this June. FDA is now working with the manufacturers of all pre-mixed 32 mg dose ondansetron injectable products (brand and generic) to voluntarily recall them from the market and anticipates that the voluntary recall will continue through early 2013.

IV. PROVIDER RECOMMENDATIONS [1, 2, 4]

- An intravenous dose of 8mg infused over 15 minutes or 0.15 mg/kg, up to a maximum of 16 mg, infused over 15 minutes may be used in adults to prevent chemotherapy induced nausea and vomiting. Subsequent doses for either dosing regimen may be given at 4 and 8 hours after the initial dose if needed.
- No single intravenous dose should exceed 16 mg due to risk of QT prolongation.
- Oral dosing recommendations as well as lower intravenous dosing recommendations remain the same.

V. REFERENCES

1. FDA Drug Safety Communication: Updated information on 32 mg intravenous ondansetron (Zofran) dose and pre-mixed ondansetron products. Safety Announcement 12-04-2012. http://www.fda.gov/Drugs/DrugSafety/ucm330049.htm . (Accessed 12-04-2012)
2. FDA Drug Safety Communication: New information regarding QT prolongation with ondansetron (Zofran). Safety Announcement 06-29-2012. http://www.fda.gov/Drugs/DrugSafety/ucm310190.htm (Accessed 12-04-2012)
3. FDA Drug Safety Communication: Abnormal heart rhythms may be associated with use of Zofran (ondansetron). Safety Announcement 09-15-2011. http://www.fda.gov/Drugs/DrugSafety/ucm271913.htm (Accessed 12-04-2012).
4. Zofran® (Ondansetron) [package insert]. Research Triangle Park, NC: GlaxoSmithKline; November 2012.

ACTIONS

- ***Facility Director*** *(or physician designee): Forward this document to the Facility Chief of Staff (COS).*
- ***Facility COS and Chief Nurse Executives:*** *Forward this document to all appropriate providers who prescribe these medications (e.g.,* ***primary care providers, oncologists, and surgery staff, including contract providers, etc****.). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.*
- ***ACOS for R&D:*** *Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).*