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

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the FDA, the 32 mg, single, intravenous (IV) dose of the anti-nausea drug ondansetron hydrochloride (Zofran®) is being withdrawn from the market due to potentially fatal cardiac risks associated with QT prolongation.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

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Sponsor</th>
<th>Application Number</th>
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</thead>
<tbody>
<tr>
<td>Ondansetron Hydrochloride Injection, USP premix in Intravia Plastic Container</td>
<td>Baxter Healthcare Corporation</td>
<td>NDA 021915</td>
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<tr>
<td>Ondansetron Hydrochloride and Dextrose in Plastic Container</td>
<td>Hospira</td>
<td>ANDA 077348</td>
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<td>Ondansetron Hydrochloride and Dextrose in Plastic Container</td>
<td>Teva</td>
<td>ANDA 077480</td>
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<td>Ondansetron Hydrochloride and Dextrose in Plastic Container</td>
<td>Bedford Labs</td>
<td>ANDA 078291</td>
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<tr>
<td>Ondansetron Hydrochloride and Dextrose in Plastic Container</td>
<td>Claris Lifesciences</td>
<td>ANDA 078308</td>
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</tbody>
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II. BACKGROUND
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).

III. DISCUSSION
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
- 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

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).