

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-198

OTHER REVIEW(S)



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

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Subject: Selected cardiac adverse events
Drug Name(s): Granisetron (Kytril, Sancuso)
Application Type/Number: NDA# 20-239, 20-305, 21-238, 22-198
Applicant/sponsor: Roche Pharmaceuticals, ProStrakan
OSE RCM #: 2008-1235

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1 INTRODUCTION

The sponsor ProStrakan has submitted an NDA for approval of granisetron transdermal system (tradename Sancuso) for the prevention of nausea and vomiting (N&V) in patients receiving highly emetogenic chemotherapy for up to 5 consecutive days. There is concern that because transdermal granisetron forms a depot in adipose tissue, it may be released variably over time in some patients and possibly increase the potential for cardiac adverse events. No cardiac adverse events were identified in the Sancuso clinical trials. It is our understanding that the sponsor has been asked to perform additional EKG studies and studies on granisetron transdermal dosage form absorption in the elderly and patients with varying body sizes, as well as the effects of heat on absorption. The MO has requested an update of selected cardiac adverse events reported to the Adverse Event Reporting System (AERS) for granisetron from the previous review of June 26, 2006 to present (see Appendix).

Granisetron and other drugs in the same class (i.e., ondansetron, dolasetron, palonosetron) are 5HT₃ serotonin antagonists used as antiemetics. These drugs have different chemical structures; however, pharmacologically they are similar.¹ The 5HT₃ serotonin antagonist drugs act on serotonin receptors found in the gastrointestinal tract which appear to play a role in the mediation of the emetic response. Selected information for 5HT₃ antiemetic drugs other than granisetron is provided in this document for informational purposes only.

Granisetron was approved in March 1995 and is indicated for prevention of postoperative n&v and cancer chemotherapy-induced N&V (the oral form also is indicated for radiation-induced N&V); the injection dosage form also is indicated for treatment of postoperative N&V. The following cardiovascular adverse events are listed in the granisetron labels: hypertension, hypotension, arrhythmias such as sinus bradycardia, atrial fibrillation, varying degrees of A-V block, ventricular ectopy including nonsustained tachycardia, and ECG abnormalities.²

2 MATERIAL REVIEWED

AERS search: *AERS search strategy:* A search of AERS was performed using *cardiac disorders* and *vascular disorders* (SOC) as MedDRA search terms and granisetron between May 1, 2006 (date of previous search) and July 15, 2008.

An SOC/PT printout was generated to identify adverse events of interest. Per discussion with the MO, any case in which the event was temporally related to a concomitant drug would be excluded from this analysis. In addition, cases in which the events were the result of their underlying condition were excluded as were cases involving labeled events. In collaboration with the MO, the following PTs were selected for review: *angina pectoris, bradycardia, cardiac arrest, cardio-respiratory arrest, cyanosis, myocardial infarction, myocardial ischaemia, tachycardia, ventricular fibrillation, pulmonary artery thrombosis, angiopathy, circulatory collapse, flushing, hypertension, hypotension, pallor, shock, and thrombosis.*

The AERS search identified 27 unduplicated reports. Of the 27 cases, 22 cases were excluded for the following reasons: Patients' cardiac events related to allergic reaction to granisetron or other concomitant medications per temporal relationship and reporter assessment (10), patients' events (hypertension, hypotension, MI, myocardial ischemia) due to underlying conditions as specified by reporter (5), event already labeled for granisetron (e.g., atrial fibrillation, angina pectoris) (2),

¹ AHFS Drug Information (on-line) version, American Society of Health-system Pharmacists, 2005.

² Kytril (granisetron hydrochloride) product label, Roche, revised November 2005.

patient's tachycardia/tremor possibly related to numerous medications including granisetron per reporter (1), patients' events (e.g., cyanosis, MI, pulmonary edema) temporally related to another drug per reporter (3), too little information provided to make causality determination (1).

Selection criteria: Five cases were included in the analysis because the patients' events were serious (e.g., cardiac arrest, QT prolongation) and the role of granisetron could not be ruled out.

TABLE 1: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF CASES OF CARDIOVASCULAR EVENTS ASSOCIATED WITH GRANISETRON USE REPORTED TO AERS BETWEEN MAY 1, 2006 AND JULY 15, 2008 (N=5)

Age (years): 65 mean, 57 median, 52 to 85 range (n=3)

Gender: Female (3), Unk (2)

Source: Foreign (5)

Year: 2006 (2), 2007 (2), 2008 (1)

Indication for use: Postoperative N&V (2), cancer chemotherapy induced N&V (2), cyclophosphamide-induced N&V (treatment of Shulman fasciitis) (1)

Dose: 0.2 mg IV, frequency not reported (1); "one ampule" IV, frequency not reported (1); IV, dose/frequency not stated (2), Not stated (1)

Onset: Approximately 24 hours (2), Unk (3)

Event (as stated by reporter; mutually exclusive): Cardiac arrest (2),[§] syncope (1),[£] QT prolongation/bradycardia (1),[#] ventricular fibrillation (1)[‡]

Outcome: Life-threatening (1), hospitalization (3)

Rechallenge: 1

Concomitant medications: 4*

Significant medical history: 1[†]

[§] One patient's cardiac arrest occurred 24 hours after granisetron administration; reporter suspects that patient may have experienced aspiration. The other case reporting cardiac arrest is described below.

[£] A follow-up CT scan was normal; no causality was found for the patient's event. Reporter specified granisetron and docetaxel as suspect medications.

[#] The reporter suspects that the patient's events were related to multiple concomitant medications including cyclophosphamide and mesna.

[‡] This patient who was using granisetron for prevention of postoperative N&V (type of surgery not specified) had underlying cardiac failure and was taking more than 15 concomitant medications, including several with known cardiotoxicity.

* At least four patients were given concomitant medications also labeled for cardiovascular adverse events (not mutually exclusive), including cyclophosphamide, docetaxel, paclitaxel, fentanyl, mesna, and midazolam.

[†] One patient had underlying aortic stenosis, coronary artery disease, and heart failure.

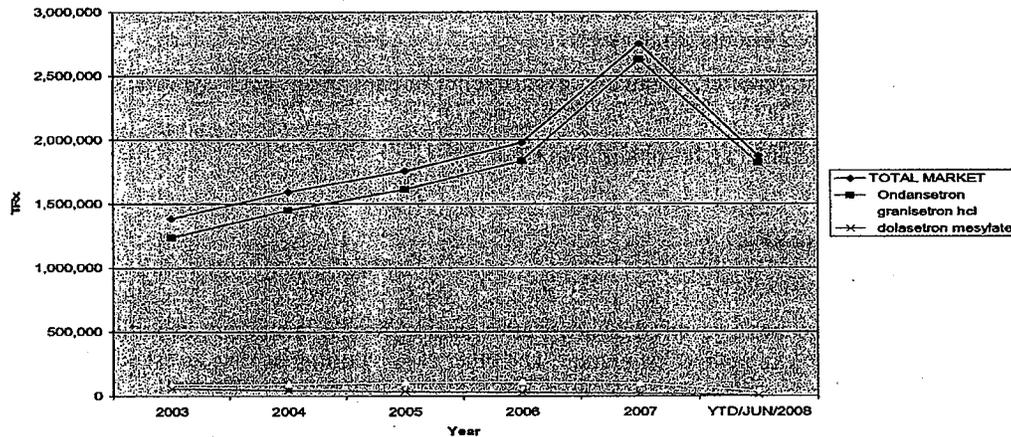
Case description: FDA# 6428783 (Foreign, 2007) A patient (age and gender not specified) experienced cardiac arrest after administration of IV granisetron (dose not specified) to treat

cancer chemotherapy-induced N&V (onset was not specified but it appeared to be soon after granisetron administration). This is a **rechallenge case**; it appeared that the patient experienced cardiac arrest when granisetron was administered with paclitaxel and again when granisetron was administered alone. The patient was successfully resuscitated both times. The patient's medical history was not reported; concomitant medications other than paclitaxel were not reported. Very little information was provided.

Literature search: Search of PubMed identified no cases of cardiovascular adverse events associated with granisetron use since the previous review of June 26, 2006.

Drug use: Drug use of the 5HT₃ antagonists is difficult to determine because ondansetron, granisetron, and dolasetron all are available orally and as an injection while palonosetron is available only as an injection (palonosetron oral dosage form was approved August 22, 2008, but is not yet marketed). OSE is unable to ascertain drug use data in oncology centers or surgery centers where many of these injectable dosage forms are administered. For information purposes only, Figure 1 depicts prescriptions dispensed for the oral dosage forms of ondansetron, granisetron, and dolasetron from January 1, 2003 through June 30, 2008.* (Ondansetron was approved in January 1991, granisetron in March 1995, dolasetron in September 1997, and palonosetron in July 2003.)

Figure 1: Total Number of Prescriptions Dispensed for Selected Oral Antiemetic Agents Through U.S. Outpatient Retail Pharmacies



Extracted August 08 (see Appendix).

* Data provided by Hina Mehta, PharmD, Drug Utilization Data Analyst, OSE Division of Epidemiology.

3 DISCUSSION

As mentioned previously, the 5HT₃ serotonin antagonist drugs act on serotonin receptors found in the gastrointestinal tract. The heart also has serotonin receptors and the potential for cardiac interaction may occur when 5HT₃ receptor antagonists are administered.³ Per granisetron labeling, granisetron's major route of metabolism is inhibited by ketoconazole, which is

³ Goodin S, Cunningham. 5-HT₃-receptor antagonists for the treatment of nausea and vomiting: a reappraisal of their side-effect profile. *The Oncologist* 2002; 7: 424-36.

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suggestive of metabolism mediated by the cytochrome P-450 3A subfamily;² this has the potential to lead to drug-drug interactions causing or contributing to cardiac adverse events.

A search of AERS identified cardiovascular adverse events for other 5HT₃ antagonists as follows (note raw data, duplicates could exist): ondansetron (300 reports), dolasetron (15 reports), and palonosetron (35 reports); these cases were reported during the time period May 1, 2006 through July 15, 2008. Ondansetron, dolasetron, and palonosetron are not available as transdermal dosage forms. Drug use data show that use of oral granisetron has increased slightly, but remains minimal compared to oral ondansetron.

4 CONCLUSIONS AND RECOMMENDATIONS

Overall, these cases provided insufficient evidence to make a determination on causality. Most patients in this case series had underlying medical history (e.g., heart failure) or were using concomitant medications (e.g., cancer chemotherapeutic agents, fentanyl) that were more likely the cause of their cardiovascular adverse events. The search did identify one rechallenge case of cardiac arrest (see Case Description), but this was a foreign case that provided very little information (DPV is unable to follow up on foreign cases). A causal role for granisetron could not be ruled out in cases described in this review. In general, granisetron and other 5HT₃ receptor antagonists are used in high-risk populations with complicated underlying conditions that could contribute to their cardiac events.

Based on AERS cases identified in this case series, it appears that cardiovascular adverse events (hypertension, hypotension, arrhythmias such as sinus bradycardia, atrial fibrillation, varying degrees of A-V block, ventricular ectopy including nonsustained tachycardia, and ECG abnormalities) are adequately reflected in the granisetron label. To further determine whether granisetron has a potential to induce cardiac arrhythmia, other studies will have to be undertaken. OSE will continue to monitor this issue.

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APPENDIX

Attachment 1: Ondansetron, granisetron, dolasetron, and palonosetron and selected cardiovascular events June 26, 2006



5HT-3 Receptor
Antagonists\Selected

Attachment 2: Database Description

_____ measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

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The _____ database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. _____ receives over _____ prescription claims per year, representing over 160 million unique patients. Since 2002 _____ has captured information on over _____ prescriptions representing 200 million unique patients.

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Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. _____ receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

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