

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 3, 2006

TO: Solomon Iyasu, MD, MPH., Acting Deputy Director
Division of Pediatric Drug Development
and
M. Dianne Murphy, M.D., Director
Office of Pediatric Therapeutics (OPT), OC

FROM: Ann Corken Mackey, R.Ph., M.P.H., Postmarketing Safety Evaluator
Division of Drug Risk Evaluation

THROUGH: Rosemary Johann-Liang, M.D., Deputy Director
for
Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation

SUBJECT: Pediatric fatalities
Drug:
Ondansetron hydrochloride (Zofran)
Injection NDA# 20-007
Tablet NDA# 20-103
Injection NDA# 20-403
Oral solution NDA# 20-6-5

Executive Summary

As requested by the Office of Pediatric therapeutics, we reviewed 18 fatal cases (raw count) associated with ondansetron hydrochloride (Zofran) use in children aged 16 years and younger (the 18 cases were identified during a BPCA review dated February 8, 2006 [see attachment A]). The time period was approval of ondansetron (January 4, 1991) up to December 1, 2004. Ondansetron is an HT₃ receptor antagonist indicated for the prevention of nausea and vomiting associated with cancer chemotherapy and prevention of postoperative nausea and/or vomiting.¹ It is indicated for use in children.¹

After excluding duplicate cases and other cases for various reasons (see AERS Search Results), we identified 7 fatalities in children possibly associated with ondansetron use. Although the role of ondansetron could not be ruled out and given the limited information available in these AERS reports, the patients' underlying medical conditions (e.g., congenital heart disease, end stage cancer, end stage cystic fibrosis, underlying renal failure, glomerulonephritis/pericarditis) and/or concomitant medications (e.g. cisapride, cyclophosphamide) were more likely causes for the patients' deaths. Ondansetron has been on the market for approximately 15 years. Drug use data could not be determined because ODS is unable to ascertain use in oncology centers or surgery centers where the injectable dosage form of ondansetron is administered. Cardiac events and rare cases of severe allergic reactions are labeled in the pediatric section of the label.

¹ Zofran (ondansetron hydrochloride) injection product label, GlaxoSmithKline, revised June 2005.

Background/Introduction

Ondansetron is an HT₃ receptor antagonist indicated for the prevention of nausea and vomiting associated with cancer chemotherapy and prevention of postoperative nausea and/or vomiting.¹ It was first approved in January 1991. It is indicated for use in children.

Relevant Product Labeling¹

Pediatric use: Little information is available about the use of ondansetron in pediatric surgical patients younger than 1 month of age. Little information is available about the use of ondansetron in pediatric cancer patients younger than 6 months of age. The clearance of ondansetron in pediatric patients 1 month to 4 months of age is slower and the half-life is approximately 2.5 fold longer than patients who are >4 to 24 months of age. As a precaution, it is recommended that patients less than 4 months of age receiving this drug be closely monitored. The frequency and type of adverse events reported in pediatric patients receiving ondansetron were similar to those in patients receiving placebo.

Adverse Reactions (Pediatric Use, Observed During Clinical Practice)

Cardiovascular: arrhythmias (including ventricular and supraventricular tachycardia, premature ventricular contraction, and atrial fibrillation), bradycardia, EKG alterations [including second-degree heart block and ST segment depression], palpitations, and syncope.

General: Flushing. Rare cases of hypersensitivity reactions, sometimes severe (e.g., anaphylaxis and anaphylactoid reactions, angioedema, bronchospasm, cardiopulmonary arrest, hypotension, laryngeal edema, laryngospasm, shock, shortness of breath, stridor) have also been reported.

Hepatobiliary: Liver enzyme abnormalities have been reported. Liver failure and death have been reported in patients with cancer receiving concurrent medications including potentially hepatotoxic cytotoxic chemotherapy and antibiotics. The etiology of the liver failure is unclear.

Local Reactions: Pain, redness, and burning at site of injection.

Lower Respiratory: Hiccups

Neurological: Oculogyric crisis, appearing alone, as well as with other dystonic reactions

Skin: Urticaria

Special Senses: Transient dizziness during or shortly after IV infusion.

Eye Disorders: Transient blurred vision, in some cases associated with abnormalities of accommodation. Rare cases of transient blindness, predominantly during intravenous administration, have been reported. These cases of transient blindness generally resolved within 20 minutes.

AERS Search Criteria

AERS was searched using the product name ondansetron (Zofran) in children ages 0 through 16 years with death as an outcome for cases reported up to December 1, 2004. The search identified 18 cases (raw data); 4 reports were duplicates leaving 14 cases for a hands-on review.

AERS Search Results

Of the 14 unduplicated fatal cases involving pediatrics, 7 cases were excluded for the following reasons: medication error (patient received Doxil instead of doxorubicin) that did not result in death (3 cases reported on one AERS form; one of the other patients died) (1), consumer report of mother who had used ondansetron during pregnancy whose infant died of unspecified cause (timeframe not reported) (1), patient's fever and abdominal pain started 12 days after last dose of IV ondansetron (patient later died of renal and liver failure) (1), patient died (blood in gastric lumen per autopsy) 17 hours after receiving ondansetron before surgery (1), patient with underlying stage IV neuroblastoma of the kidney who had received ondansetron along with other cancer chemotherapeutic agents developed multiorgan failure and died (per reporter, his death was not related to ondansetron) (1), consumer report of patient with underlying medulloblastoma who received IV ondansetron along with radiation and chemotherapy died of a brain tumor (1),

and study report in which investigator stated that patient died of worsening idiopathic pneumonitis with progressive germ cell disease (1). The remaining 7 cases are described below.

DEMOGRAPHIC DATA OF FATAL CASES ASSOCIATED WITH ONDANSETRON USE IN PEDIATRIC PATIENTS REPORTED TO AERS UP TO December 1, 2004 (n=7)

Age: 9 months to 2 years (2), 10 to 11 years (2), 14 to 16 years (3)
Gender: Male (4), female (3)
Year: 1993 (1), 1996 (1), 1997 (1), 2001 (4)
Source: Domestic (3), foreign (4)
Indication for use:* treatment of nausea/vomiting (5), prevention of nausea/vomiting (1), Unk (1)
Dose: 2 mg IV (1), 4 mg IV (1), 0.15 mg/kg (1), dose unk IV (1), 4 mg oral (1), 3 mg route unk (1), 6 mg route unk (1)
Onset: 1 dose (3), 2 days (1), 17 days (1), "numerous" (1), unk (1)
Underlying medical history: congenital heart disease (1), end stage cystic fibrosis (1), stage IV rhabdomyosarcoma (1), renal failure due to severe bilateral renal hypoplasia (1), LFA-1 deficiency/3 bone marrow allografts/cytomegaloviral infection/probable graft versus host reaction (1), disseminated lupus/glomerulonephritis/nephrotic syndrome/pericarditis (1)
Concomitant medications:[†] 6

* Indication for use as stated in report.

[†] Six patients were taking concomitant medications including (not mutually exclusive): Alfacalcidol, cefuroxime, cisapride, clarithromycin, cyclophosphamide, etoposide, ganciclovir, ifosfamide, morphine, and sodium polystyrene sulfonate.

All 7 cases are described below:

Case# 5059242 (Foreign, 1993) A 14-year-old female **became unresponsive, had decreased respiratory rate, decreased blood pressure, and decreased oxygen saturation** about an hour after receiving a single dose of 4 mg of IV ondansetron to treat nausea. She also had received morphine and cyclizine in the hours leading up to the ondansetron injection. She was intubated, but remained unresponsive and died 6 days later. Cause of death at post mortem was hypoxic brain damage. The day before, she had undergone surgery for correction of scoliosis and had received anesthesia without complication. She had a history of mild asthma and hay fever; concomitant medications included albuterol, beclomethasone dipropionate, and terfenadine.

Case# 5373212 (Domestic, 1996) A 10-year-old male with underlying stage IV rhabdomyosarcoma became **dizzy, collapsed, and died** soon after receiving 0.15 mg/kg of IV ondansetron and 4 mg/kg of methylprednisolone (third day of sixth cycle) to treat chemotherapy-induced nausea. Resuscitation attempts were unsuccessful. Per death certificate, the cause of death was rhabdomyosarcoma. He had received both ondansetron and methylprednisolone numerous times prior to the time of arrest and did not experience any adverse effects. Concomitant medications included mesna, ifosfamide, and etoposide.

Case# 3121163 (Foreign, 1997) A 9-month-old male died of **acidosis, bundle branch block, and cardiac arrest (with QT prolongation)** after receiving numerous medications including cisapride and ondansetron (6 mg a day, duration not reported) to treat vomiting and colitis. His medical history included LFA-1 deficiency, 3 bone marrow allografts, cytomegaloviral infection, and probable graft versus host reaction. Concomitant medications included cyclosporin, ganciclovir, omeprazole, amikacine hydrocortisone, cyclophosphamide, foscarnet, alizapride, tienam, and ornidazole.

Case# 3706367 (Foreign, 2001) A 16-year-old female died due to "**septic shock or cardiomyopathy (associated with cyclophosphamide)**" 3 days after receiving an unknown dose of IV ondansetron to prevent nausea. One day after ondansetron therapy was discontinued, she developed fever, hypotension, shivers, thoracic pain and sinus tachycardia; she later

developed dyspnea, cephalgia, and profuse diarrhea. Septic shock was suspected; cardiac ultrasound showed worsening pericardial effusion. She experienced two cardiac arrests, respiratory failure, pulmonary "swamping," and died despite resuscitation attempts. The patient had numerous underlying medical conditions including disseminated lupus erythematosus, glomerulonephritis, nephrotic syndrome, decreased complement C4, pericarditis, and lymphopenia. She had been hospitalized for allograft including stem cells. Concomitant medications included prednisone, cyclophosphamide, mesna, dextropropoxyphene/paracetamol combination, furosemide, alizapride, and ergocalciferol.

Case# 3677854 (Foreign, 2001) A 2-year-old male with a history of renal failure due to severe bilateral renal hypoplasia was **found lifeless in bed (cause of death unknown)**; he had received 3 mg of oral ondansetron a day for 17 days to treat nausea and vomiting. His medical history included Nissen operation for esophageal reflux. Concomitant medications included sodium polystyrene sulfonate, alfacalcidol, erythropoietin, calcium supplements, and growth hormone.

Case #4021506 (Domestic, 2003) An 11-year-old female experienced **decreased oxygen saturation, headache, dizziness, and respiratory failure** 1 hour after receiving one 4 mg dose of IV ondansetron; she died 3 hours later. She was receiving IV cefuroxime and oral clarithromycin (she had received oral clarithromycin prior to and during hospitalization). Her medical history included congenital heart disease, nausea of unknown etiology, and allergy to amoxicillin and codeine.

Comment on Case #4012506: *This case raises some questions because there is no information on how clinically affected she was from her underlying "congenital heart disease," and whether she was hospitalized and being treated for her heart condition when she experienced respiratory failure. Her concomitant meds (both antibiotics) suggest that she may have been undergoing treatment for some type of lower respiratory infection (i.e. pneumonia) in which case respiratory failure on top of her underlying "congenital heart disease" may have been the main cause of death. However, we cannot exclude the possibility that both clarithromycin, which has cardiac toxicity, in conjunction with ondansetron may have contributed to her demise. We have no further information.*

Case# 4118456 (Domestic, 2003) a 16-year-old male with underlying end stage cystic fibrosis developed "**oxygen saturation and arrested**" minutes after receiving a single dose of 2 mg IV ondansetron to treat nausea. The patient was in the hospital when he received ondansetron. He had a history of numerous allergies to various foods and "medications (especially antibiotics);" he had undergone tobramycin desensitization process. (Attorney report providing little information.)

Overall Comment: *Aside from the further commented case #4021506 above, the 6 remaining cases show young patients who received ondansetron in the setting of complicated underlying medical conditions and/or multiple concomitant medications.*

Summary

After excluding duplicate cases and other cases for various reasons (see AERS Search Results), we identified 7 fatalities in children possibly associated with ondansetron use. Although the role of ondansetron could not be ruled out and given the limited information available in these AERS reports, the patients' underlying medical conditions (e.g., congenital heart disease, end stage cancer, end stage cystic fibrosis, underlying renal failure, glomerulonephritis/pericarditis) and/or concomitant medications (e.g. cisapride, cyclophosphamide) were more likely causes for the patients' deaths. Ondansetron has been on the market for approximately 15 years. Drug use data could not be determined because ODS is unable to ascertain use in oncology centers or surgery centers where the injectable dosage form of ondansetron is administered. Cardiac events and rare cases of severe allergic reactions are labeled in the pediatric section of the label.

Ann Corken Mackey 5/3/06

Ann Corken Mackey, R.Ph., M.P.H.
Safety Evaluator

Concur:

Lanh Green 5/3/06

Lanh Green, Pharm.D., M.P.H.
Safety Evaluator Team Leader

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ann Corken
5/4/2006 09:55:09 AM
PHARMACIST

Rosemary Johann-Liang
5/4/2006 10:47:28 AM
MEDICAL OFFICER