

MEMORANDUM

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

DATE: February 8, 2006

FROM: Ann Corken Mackey, R.Ph., M.P.H.
Postmarketing Safety Evaluator
Office of Drug Safety
Division of Drug Risk Evaluation, HFD-430

THROUGH: Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation, HFD-430

TO: Solomon Iyasu, MD, MPH., Team Leader
Division of Pediatric Drug Development, HFD-960
Office of Counter-Terrorism and Pediatric Drug Development, HFD-950

SUBJECT: One Year Post-Pediatric Exclusivity Postmarketing Adverse Event
Review (PID# D040850)
Ondansetron hydrochloride (Zofran)
Injection NDA# 20-007
Tablet NDA# 20-103
Injection NDA# 20-403
Oral solution NDA# 20-6-5
Pediatric Exclusivity Approval Date: January 1, 2005

Executive Summary

As requested by the Office of Counter-Terrorism and Pediatrics, we reviewed the pediatric adverse events in association with the use of ondansetron hydrochloride (Zofran) in children aged 16 years and younger. The time period of interest was the one-year period (the search period is expanded to 13 months to allow for the time lag needed to collect 12 months of data) following FDA Pediatric Exclusivity approval, December 1, 2004 through January 1, 2006.

For the 12-month time period after pediatric exclusivity was granted, we identified 20 adverse events in children 16 years of age and younger. The AERS search identified one fatal case providing little information, allergic reactions/anaphylaxis (n=4), neurologic events (n=5), hepatic events (n=2), bradycardia/respiratory depression (n=1), and miscellaneous adverse events (n=7) in patients using ondansetron, primarily the injectable dosage form. Some cases provided very little information; most of the cases were from foreign sources. In general, most of the patients in this case series had underlying conditions and/or were receiving concomitant medications making it difficult

to relate their outcomes to ondansetron use. Allergic reaction/anaphylaxis, neurologic adverse events, and hepatic adverse events are labeled for ondansetron. Respiratory depression and bradycardia are not labeled; however, the foreign case provided very little information.

AERS Search Results: Ondansetron hydrochloride (Zofran)

AERS Search Dates: Searches for U.S. and foreign cases during the following time periods, (1) January 4, 1991 (approval date) to December 1, 2004 and (2) December 1, 2004 (pediatric exclusivity date) to January 1, 2006.

A. Adverse events from marketing approval date, January 4, 1991 to December 1, 2004:

1. Raw counts of reports: Table 1 (parentheses denote U.S. origin report counts)

	All reports (US)	Serious (US)	Death (US)
All ages	3180 (2373)	1435 (656)	204 (79)
Adults (≥17)	2075 (1398)	1145 (487)	165 (55)
Peds (0-16)	204 (148)	126 (74)	18 (11)
Null values	901 (827)	164 (95)	21 (13)

Figure 1: Reporting trend for pediatric reports from approval date:

<u>Year</u>	<u>Report count</u>
1991	36
1992	32
1993	15
1994	11
1995	10
1996	15
1997	13
1998	6
1999	6
2000	10
2001	10
2002	17
2003	9
2004	14

2. Counts of top 20 reported event preferred terms for all ages, adults, and pediatric age groups (underscore denotes unlabeled events).

All ages: Vomiting (269), dizziness (212), headache (212), drug ineffective (183), amblyopia (172), hypotension (139), dyspnoea (135), nausea (128), pruritus (117), dermatitis (114), pyrexia (113), chest pain (104), urticaria (94), visual disturbance (91), convulsion (89), vasodilation (82), hypersensitivity (75), injection site hypersensitivity (75), confusional state (74), drug interaction (74)

Adults: Vomiting (172), dizziness (139), headache (137), amblyopia (119), dyspnea (113), hypotension (111), pruritus (99), nausea (95), pyrexia (93), chest pain (92), drug ineffective (87), dermatitis (81), urticaria (68), tachycardia (58), convulsion (57), tremor (55), hypertension (54), vasodilation (53), hypersensitivity (52), abdominal pain (50)

Peds: Vomiting (26), dyspnoea (14), hepatic function abnormal (12), hypotension (11), confusional state (10), pyrexia (9), urticaria (9), convulsion (8), drug interaction (8), dystonia (8), grand mal convulsion (8), abdominal pain (7), anaphylactoid reaction (7), asthma (7), drug ineffective (7), headache (7), pancreatitis (7), vasodilation (7), cough (6), extrapyramidal disorder (6)

B. From Pediatric Exclusivity approval date through AERS cut-off date (January 1, 2006):

1. Raw counts of reports: Table 2

	All reports (US)	Serious (US)	Death (US)
All ages	338 (145)	256 (68)	27 (10)
Adults (≥17)	238 (75)	201 (42)	22 (6)
Peds (0-16)	20 (8)	16 (5)	1 (0)
Null values	80 (62)	39 (21)	4 (4)

2. Counts of top 20 reported event preferred terms for all ages, adults, and pediatric age groups including identifying events not previously described in the label (underscore denotes unlabeled events).

All ages: Drug exposure during pregnancy (45), nausea (33), vomiting (33), drug ineffective (30), dyspnea (22), pyrexia (17), pruritus (15), dystonia (14), rash (13), cardiac arrest (11), hypotension (11), confusional state (10), dyskinesia (10), headache (10), toxic epidermal necrolysis (10), abdominal pain (9), constipation (9), loss of consciousness (9), bradycardia (8), cardio-respiratory arrest (8)

Adults: Nausea (25), vomiting (23), drug exposure during pregnancy (19), dyspnoea (19), drug ineffective (17), pyrexia (17), pruritus (14), cardiac arrest (11), rash (11), dystonia (10), toxic epidermal necrolysis (10), hypotension (9), loss of consciousness (9), abdominal pain (8), cardio-respiratory arrest (8), dyskinesia (8), bradycardia (7), chest pain (7), chills (7), confusional state (7)

Peds: Headache (3), convulsion (2), cyanosis (2), drug exposure during pregnancy (2), drug ineffective (2), dyspnoea (2), hypotension (2), musculoskeletal stiffness (2), nausea (2), vomiting (2), agitation (1), anaphylactic shock (1), ascites (1), aspartate aminotransferase increased (1), bradycardia (1), bronchospasm (1), congenital foot malformation (1), constipation (1), cough (1), dehydration (1)

Postmarketing hands-on review of all peds adverse event reports from all sources received during the one-year after a drug receives pediatric market exclusivity.

Summary

For the 12-month time period after pediatric exclusivity was granted, we identified 20 cases specifying adverse events in children 16 years of age and younger.

This search identified one case involving a 3-year-old male who received 4 mg ondansetron tablets (indication and duration unknown) and died; the reported provided very little information including cause of death (foreign report).

Four cases reported suspected allergic reactions/anaphylaxis in pediatric patients using ondansetron. The cases are summarized as follows: maculopapular rash in a 12-year-old girl who received morphine and rocuronium bromide concomitantly (foreign case, n=1); cyanosis, hypotension, and urticaria with positive skin test for ondansetron and codeine in a 4-year-old female (foreign case, n=1); dyspnea, hypotension, and pruritus in a 15-year-old male who received methotrexate, aprepitant, and dexamethasone concomitantly (n=1); and anaphylactic shock in a 31-month-old female who received alizapride (antiemetic) concomitantly in her second cancer chemotherapy treatment (the patient recovered; foreign case; n=1). Three of the four patients received ondansetron IV (route of administration unknown for one case).

Five cases described pediatric patients who developed neurologic adverse events possibly associated with ondansetron use. A 3-year-old female experienced a dystonia reaction and agitation after receiving ondansetron IV, an unspecified antibiotic, and an unspecified anesthetic agent; ondansetron treatment continued and the events were unresolved at the time of the report. A 10-year-old girl with underlying gastroenteritis developed auditory hallucinations, dry mouth, headache, and blurred vision after receiving 12 mg ondansetron IV a day for 3 days; the events resolved. A 4-year-old male developed seizure, hypotonia, musculoskeletal stiffness, and urinary incontinence after receiving 2 mg ondansetron IV (single dose); the events resolved (foreign case). A 10-year-old girl with an underlying urinary tract infection developed extrapyramidal reaction, speech impairment, and clenched jaw after receiving a single dose of 4 mg ondansetron IV; she was receiving promethazine and prochlorperazine concomitantly. A 15-year-old boy developed seizure and oculogyric crisis after taking 4 mg of ondansetron IV a day for 6 days; concomitant medications included paracetamol, tramadol, miconazole, codeine, and morphine (foreign case).

Two cases identified in this search involved hepatic adverse events (both cases are from foreign sources). One 6-year-old girl experienced increased aspartate aminotransferase (values not provided) after using etanercept, methotrexate, naproxen, and oral ondansetron to treat juvenile arthritis (patient outcome and dose/duration for ondansetron not provided). A 9-year-old boy experienced increased alanine aminotransferase, ascites, and pleural effusion after receiving several cancer chemotherapy agents and ondansetron (4 mg per day, duration/route of administration not provided) to treat neuroblastoma; the patient was treated and was improving at the time of the report.

A 1-year-old child (gender not specified) experienced respiratory depression and bradycardia after receiving a single 2-mg dose of ondansetron IV to treat an unknown condition; very little information was provided (foreign case).

Seven cases involved miscellaneous events as follows: birth defects (i.e., foot/limb malformations and trachial malaisa) in infants whose mothers had used ondansetron during pregnancy (n=2), possible precipitation of ondansetron and amoxicillin and clavulanate combination in IV in a 15-year-old male who was having surgery (patient outcome not reported) (n=1), ondansetron not effective in controlling the patients' nausea/vomiting (n=2), and nonserious labeled adverse events (i.e., headache and constipation) (n=2). Two of these cases were from foreign sources.

The AERS search identified one fatal case providing little information, allergic reactions/anaphylaxis (n=4), neurologic events (n=5), hepatic events (n=2), bradycardia/respiratory depression (n=1), and miscellaneous adverse events (n=7) in patients using ondansetron, primarily the injectable dosage form. Some cases provided very little information; most of the cases were from foreign sources. In general, most of the patients in this case series had underlying conditions and/or were receiving concomitant medications making it difficult to relate their outcomes to ondansetron use. Allergic reaction/anaphylaxis, neurologic adverse events, and hepatic adverse events are labeled for ondansetron. Respiratory depression and bradycardia are not labeled; however, the foreign case provided very little information.

Ann Corken Mackey 2/8/06

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

Concur:

Lanh Green 2/8/06

Lanh Green, Pharm.D., M.P.H.

Appendix

Standard Searches:

- A. Adults (17 yrs and above)
 - 1. All outcomes from AP date (no set criteria)
 - 2. Serious outcomes from AP date
 - 3. Death as an outcome from AP date
 - 4. All outcomes from PE date to present or any desired date
 - 5. Serious outcomes from PE date to present or any desired date
 - 6. Death as an outcome from PE date to present or any desired date

- B. Ages 0-16 yrs ONLY
 - 1. Same as above 1-6
 - 2. Retrieve case reports for hands-on review

Standard Printouts for Attachments:

- A. Adults (17 yrs and above)
 - 1. Frequency counts of all preferred terms (PT) in cases
 - 2. Frequency counts of all PT in cases with serious outcomes
 - 3. Frequency counts of all PT in cases with death as an outcome
 - 4. Frequency counts of cases by Gender and ages

- B. Ages 0-16 yrs ONLY
 - Same as above 1-4

Drug Product Information

Limitations of the Adverse Event Reporting System (AERS)

AERS collects reports of adverse events from health care professionals and consumers submitted to the product manufacturers or directly to the FDA. The main utility of a spontaneous reporting system, such as AERS, is to identify potential drug safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

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/s/

Ann Corken
2/9/2006 11:11:23 AM
PHARMACIST

Mark Avigan
2/14/2006 01:45:59 PM
DRUG SAFETY OFFICE REVIEWER