<table>
<tr><td>DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINSTRATION</td><td colspan="2">DDRE POSTMARKETING SAFETY REVIEW</td></tr>
<tr><td>TO: Lisa L. Mathis, M.D.,
OND Associate Director
Pediatric and Maternal Health Team
Office of New Drugs (OND), CDER
and
M. Dianne Murphy, M.D., Director
Office of Pediatric Therapeutics (OPT), OC</td><td>FROM: Ronald Wassel, Pharm.D.
Safety Evaluator
Division of Drug Risk Evaluation</td><td>RCM # 2006-74
(PID # D060311)
December 21, 2006</td></tr>
<tr><td>THROUGH: Rosemary Johann-Liang, M.D.,
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for
Mark Avigan, M.D., C.M.,
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Division of Drug Risk Evaluation</td><td colspan="2">REQUESTOR/phone #: Debbie Avant
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301-796-1642</td></tr>
<tr><td colspan="3">DRUG: Zyvox® (linezolid)</td></tr>
<tr><td>THERAPEUTIC CLASSIFICATION:
Oxazolidinone (synthetic antibiotic)</td><td>NDA/IND: # 21-130, 21-131, 21-132</td><td>SPONSOR: Pfizer</td></tr>
<tr><td colspan="3">EVENT: Cardiac events (arrhythmias) in adult and pediatric patients</td></tr>
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Executive Summary: As part of the one-year post-exclusivity adverse event reporting for linezolid, the Pediatric Team reviewed serious adverse events in pediatric patients (0-16 years) since linezolid's market approval (4/18/2000). Their review identified a total of nine pediatric patients with cardiac adverse events and an additional search for cardiac arrhythmias in all ages identified 104 reports (crude count). To further characterize the cardiac risk of linezolid, the Pediatric Team requested a review from the Division of Drug Risk Evaluation (DDRE) to look at cases of cardiac arrhythmias in adult and pediatric patients exposed to all forms of linezolid since its market approval to evaluate if there is a safety signal.

Both a WebVDME (data mining) analysis and an AERS search were conducted for linezolid for cardiac arrhythmias. The WebVDME search using an EB05 ≥2 as a signal definition (indicating a 95% confidence that the drug-event is occurring at least at twice the expected rate when considering all other drugs and events in the database) found zero results. Repeating the search using an EB05 score of greater than 1 as a signal definition (indicating a 95% confidence that the drug-event in question occurs at least at a higher-than-expected rate) found only one result for tachycardia with an EB05 score of 1.42 based on an N of 36 non-adjudicated cases. The AERS search retrieved 111 reports (96 unduplicated). Of these, 73 were excluded because other factors more likely contributed to the cardiac event. Fifteen of the excluded cases reported serotonin syndrome. The remaining 23 non-excluded cases included 11 cases of tachycardia, 6 cases of bradycardia, 3 cases of an arrhythmia, and 1 case each of atrial fibrillation, asystole, and torsade de pointes.

Cardiotoxicity was not identified during the pre-approval safety review of linezolid. Data mining analysis using WebVDME failed to show an association between linezolid and cardiac arrhythmias, although absence of an increased signal score does not rule out a potential drug-event association. The AERS search for cardiac arrhythmias retrieved 96 unduplicated cases, but the majority (73) could be considered related to other causes, primarily serotonin syndrome. Even in the cases that could not be excluded because there was a temporal relationship, details were often lacking making assessment difficult, and in several others, alternative explanations could be considered. Many of the cases were from foreign sources and lacked adequate information. The case submitted as torsade de pointes (TdP) also lacked detailed information and it was noted the patient had an unspecified cardiac disorder. Given the lack of a data mining signal together with the paucity of quality cases in AERS, the available data does not support a safety signal for cardiotoxicity with linezolid at this time.

We will continue to monitor reports for linezolid to determine any changes.

Reason for Request/Review: As part of the one-year post-exclusivity adverse event reporting for linezolid, the Pediatric Team reviewed serious adverse events in pediatric patients (0-16 years) since linezolid's market approval (4/18/2000). Their review identified a total of nine patients with cardiac adverse events. They included three cases of abnormal heart rhythm, two cases of tachycardia, two cases of cardiac arrest/collapse, and two cases of edema. The Pediatric reviewer conducted an additional search for cardiac arrhythmias with linezolid in all ages and identified 104 patient reports (crude count).

DDRE's review of adverse events in pediatric patients related to linezolid in the one–year pediatric exclusivity period (2/11/2005 to 3/11/2006) identified six cases that were cardiac in nature (included in the nine obtained by the Pediatric Team).[1] A search for additional pediatric cardiac events outside the exclusivity period did not find any meaningful cases.

Linezolid has not been thought to be cardiotoxic. However, to further characterize the cardiac risk of linezolid, Pediatrics requested a review to look at cases of cardiac arrhythmias in adult and pediatric patients exposed to all forms of linezolid since its market approval to evaluate if there is a safety signal.

Relevant Product Labeling: None

Search Date: 9/25/2006 (AERS) 11/13/2006 (WebVDME)	**Search Type(s):** ☒ AERS SRS Literature ☒ Other—WebVDME (data mining)

Search Criteria:

WebVDME was searched with linezolid against MedDRA High Level Group Term Cardiac Arrhythmias.

AERS was searched with linezolid against the MedDRA High Level Group Term Cardiac Arrhythmias for cases with an FDA received date of 4/1/2000 through 9/15/2006, inclusive.

Data Mining Background: The data mining analysis evaluates the records contained in AERS and then quantifies potential drug-event associations by producing a ranked set of values or scores which indicate varying strengths of reporting relationships between drugs and events.[2] These scores, denoted by the Empirical Bayes Geometric Mean (EBGM), provide a stable estimate of the relative reporting rate of an event for a particular drug relative to all other drugs in the database being analyzed. The analysis also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95 respectively.

An EBGM of 1 indicates that the particular drug-event combination occurs together as often as would be expected under the assumption of randomly paired drug and event reports (independence assumption). Using an EB05 score of greater than 1 as a signal definition corresponds to being 95% confident that the drug-event in question occurs at least at a higher-than-expected rate. An EBGM value of greater than 2 ensures with a high probability that the particular drug-event occurs in these patient data records at least twice as often as expected under the independence assumption. Using an EB05 ≥ 2 as a signal definition indicates 95% confidence that the drug-event is occurring at least at twice the expected rate when considering all other drugs and events in the database.

The higher the EB05 score, the higher the association between the drug and event, as reported in the database being analyzed. **Note that this "association" is a factor of the relative reporting of various events among all drugs in the database and that it does not automatically imply causality. Signal scores indicate higher-than-expected drug-event reporting associations, not necessarily causality or the degree of risk.**

Search Results:

WebVDME—A search using an EB05 ≥2 as a signal definition (indicating a 95% confidence that the drug-event is occurring at least at twice the expected rate when considering all other drugs and events in the database) found zero results. Repeating the search using an EB05 score of greater than 1 as a signal definition (indicating a 95% confidence that the drug-event in question occurs at least at a higher-than-expected rate) found only one result for tachycardia with an EB05 score of 1.42 based on an N of 36 non-adjudicated cases.

AERS—The search retrieved 111 reports (96 unduplicated). Of these, 73 were excluded in which other factors more likely contributed to the cardiac event. There were 15 cases of serotonin syndrome. Other confounding causes included:

- other drugs
- poor temporal relationship
- septic/hypovolemic shock
- acidosis
- negative rechallenge or dechallenge
- no actual adverse event/miscoded
- pre-existing condition
- cases of cardiac arrest/sudden death resulting from disease progression (final cause of death)
- anemia
- endocarditis/valve rupture
- miscellaneous (hypokalemia, tracheostomy/intubation, burns, volume overload, insufficient information)

The remaining 23 cases were classified as follows:

- tachycardia 11
- bradycardia 6
- arrhythmia 3
- atrial fibrillation 1
- asystole 1
- torsade de pointes 1

Demographics (n=23):

Age (n=14):	Range—6 to 84 years; Median—43 years; Mean—44 years
Gender (n=17):	Male—11; Female—6
Source:	Domestic—13; Foreign—10
Route:	Intravenous—14; Oral—9
Outcome:	Hospitalized patient (n=18): Recovered—5; Prolonged—4; Unknown—9
	Outpatient (n=5): Recovered—3; Unknown—2

Review of Cases: Cases involving pediatric patients were presented in the previous consult and will not be detailed here.[1] In summary, six cases were identified in which three reported tachycardia, and there was one report each for chest pressure with an irregular heart beat, an abnormal electrocardiogram, and an arrhythmia. These cases, although temporally related, could not be definitively associated with linezolid as other factors may have been involved.

Tachycardia (n=11)—Several of the cases had limited information and lacked essential details such as medical history and concomitant medications making assessment difficult (e.g. "… patient experienced increased heart rate after starting Zyvox. No further information given.").

A case involving a 38–year–old male (ISR# 4633795-2; US) was actually submitted because of a hemorrhage thought to be secondary to linezolid–induced thrombocytopenia, although the narrative noted the patient developed supraventricular tachycardia requiring treatment with amiodarone and external pacing until an internal pacemaker was placed. However, this patient had congenital heart disease and was status-post tricuspid valvuloplasty, placement of a porcine valve, and a MAZE procedure with post-op atrial flutter one month prior to the event, which is a more likely explanation for the arrhythmia.

A 30–year–old female (ISR# 4280400-3; US) reported that an hour following an infusion of linezolid, she developed ventricular tachycardia that lasted about 10 seconds, and had premature ventricular contractions (PVCs) at about 30 per minute for the next hour. She was maintained on linezolid without further incident and was switched to oral therapy upon discharge. After three days of oral therapy she again experienced PVCs on exertion. Her medical history includes angina, coronary artery disease, multiple sclerosis, hypertension, one incident of respiratory failure, and one incident of respiratory distress. Concomitant medications include Cardizem, Imuran, Paxil, Uniretic, K-Dur, Compaxone, and Xanax. Per the report, her underlying cardiovascular condition and concomitant medications are considered more likely explanations for the events.

An 84–year–old male (ISR# 4008641-0; Great Britain) developed tachycardia, diarrhea, disseminated intravascular coagulation, hypotension, and a rash while receiving linezolid. The patient had also received a single dose of teicoplanin prior to these events. This might represent an allergic reaction to linezolid or teicoplanin.

Bradycardia (n=6)—As with the cases of tachycardia, most of the reported cases had limited information and lacked essential details such as medical history and concomitant medications making assessment difficult. One reported the patient was taking digoxin concomitantly, and another stated that the patient's physician did not think linezolid was the cause.

A 34–year–old male (ISR# 3772141-3; Great Britain) with 50% steam burns, a fractured leg, and acute renal failure received linezolid due to a VRE infection. Concomitant medications included ramipril, nystatin, chloramphenicol, and meropenem. The patient experienced bradycardia that required an increase of inotropes. Although linezolid cannot be excluded due to the temporal time sequence, the patient's underlying conditions and/or concomitant medications might be co-causal factors.

A 49–year–old female (ISR# 4332711-0; Italy) with a history of cancer of the biliary tree was hospitalized for fever and jaundice. Ceftazidime and linezolid were started empirically, which was changed to imipenem and linezolid after 72 hours based on blood cultures. Two days later the patient's blood pressure increased and was associated with severe bradycardia (37-40 beats/min). Linezolid was ceased and the pulse rate became normal after about 48 hours. This case was reported in the literature and the authors considered the bradycardia more likely related to linezolid than to the patient's jaundice, which has been associated with bradycardia.[3]

Review of Cases (cont):

Other cardiac events—

A 40–year–old male (ISR# 4526331-2; Germany) suffering from grade II-III burns over 45% of his body received linezolid for MRSA infection. On an unspecified date he developed *arrhythmias, heart block, asystolic phases* and *tachycardia*. The events were first documented on [redacted] and linezolid was discontinued on [redacted] after which the arrhythmias improved. The patient's history was significant for diabetes, and concomitant medications included multibionta, selenium, zinc dl-aspartate, tocopherol, acetylcysteine, activated dimeticone, ibuprofen, pantoprazole, heparin, nystatin, ascorbic acid, insulin, and piritramide.

A 56–year–old male (ISR# 4503086-9; Great Britain) received oral linezolid at an unknown dosage and frequency for an unknown indication for 7-10 days. On an unknown date the patient developed *cardiac arrhythmias* and then went on to have a cardiac arrest twice. The patient was described as a renal patient. It was reported the arrhythmias ceased when linezolid was withdrawn.

A 70–year–old male (ISR# 4091266-9; Great Britain) with an unknown medical history was treated with linezolid for an unknown reason while in the ICU. On an unknown date the patient developed *asystole*. Outcome is unknown.

A 66–year–old male (ISR# 3508564-7; Greece) started study treatment with linezolid and on the last date of treatment, *atrial fibrillation* was noted on the patient's monitor. Amiodarone was administered and the patient recovered. The patient was also receiving salbutamol, which offers an alternative explanation.

A male of unknown age (ISR# 3800730-6; US) with MRSA bacteremia received vancomycin for 10 days and then was switched to linezolid. After two days, the patient developed *torsade de pointes* and had to be shocked. No other information was provided. Medical history included chronic obstructive airways disease and an unspecified cardiac disorder. Concomitant medications were not listed.

Findings/Conclusions: Linezolid has not been thought to be cardiotoxic and cardiotoxicity was not identified during the pre-approval safety review of linezolid. Data mining analysis using WebVDME failed to show an association between linezolid and cardiac arrhythmias, although absence of an increased signal score does not rule out a potential drug-event association. The AERS search for cardiac arrhythmias retrieved 96 unduplicated cases, but the majority (73) could be considered related to other causes, primarily serotonin syndrome. Even in the cases that could not be excluded because there was a temporal relationship, details were often lacking making assessment difficult, and in several others, alternative explanations could be considered. Many of the cases were from foreign sources and lacked adequate information. The case submitted as torsade de pointes (TdP) also lacked detailed information and it was noted the patient had an unspecified cardiac disorder. Given the lack of a data mining signal together with the paucity of quality cases in AERS, the available data does not support a safety signal for cardiotoxicity with linezolid at this time.

We will continue to monitor reports for linezolid to determine any changes.

Reviewer's Signature / Date: **Ronald Wassel, Pharm.D.** **11/15/06**	**Team Leader's Signature / Date:** **Melissa Truffa, R.Ph.** **12/18/06**

Reference:

1. Memorandum dated June 23, 2006. From Ronald Wassel to Lisa Mathis and M. Diane Murphy. One-year Post-Pediatric Exclusivity Postmarketing Adverse Event Review for Linezolid (Zyvox®).
2. Szarfman A, Machado SG, O'Neill RT. Use of Screening Algorithms and Computer Systems to Efficiently Signal Higher-Than-Expected Combinations of Drugs and Events in the US FDA's Spontaneous Reports Database. Drug Safety 2002; 25:381-392.
3. Tartarone A, Gallucci G, Iodice G, et al. Linezolid–induced bradycardia: a case report. Int J Antimicrob Agents 2004; 23:412-3.

cc: NDA # 21-130, 21-131, 21-132
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CDER/OSE/DDRE Avigan / Johann-Liang / Truffa / Milburn / Chron / Drug
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/s/

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12/21/2006 10:47:33 AM
DRUG SAFETY OFFICE REVIEWER

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MEDICAL OFFICER