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

Date:	August 8, 2008
To:	Lisa L. Mathis M.D., Associate Director Pediatric and Maternal Health Staff (PMHS) Office of New Drugs (OND), CDER and M. Dianne Murphy, M.D., Director Office of Pediatric Therapeutics (OPT), OC
From:	Ronald Wassel, Pharm.D., Safety Evaluator Division of Pharmacovigilance II
Through:	Melissa Truffa, R.Ph., Team Leader Division of Pharmacovigilance II
	Ann McMahon, M.D., M.S., Acting Director Division of Pharmacovigilance II Office of Surveillance and Epidemiology (OSE), CDER
Subject:	Update of cardiac events (arrhythmias) in adult and pediatric patients
Drug Name(s):	Zyvox® (linezolid)
Application Type/Number:	NDA 21-130, 21-131, 21-132
Applicant/sponsor:	Pfizer
OSE RCM #:	2008-675

EXECUTIVE SUMMARY

The Office of Pediatric Therapeutics (OPT) requested an updated Adverse Event Reporting System (AERS) search to identify if there have been any additional cardiac adverse events (arrhythmias) for adults and pediatrics for linezolid since a December 2006 review.

A data mining analysis of cardiac arrhythmias for linezolid compared to other drugs in the AERS database using an EB05 score of ≥ 1 found only tachycardia with an EB05 score of 1.37 based on an N of 42 non-adjudicated cases (this compares to an EB05 score of 1.42 with an N of 36 in the 2006 review). Typically, an EB05 ≥ 2 is used to identify potential signals, but these EB05 scores were all < 2.

The AERS update retrieved 35 new unduplicated cases; however, 28 were assessed as unrelated, or not cases of a direct cardiotoxic effect of linezolid. The remaining seven cases (tachycardia, paroxysmal supraventricular tachycardia, ventricular tachycardia, abnormal electrocardiogram, and three cases of QT prolongation) could not be definitively attributed to linezolid as there were other, more likely explanations, or insufficient information to make an assessment.

Consistent with the previous review, the available data from AERS and data mining do not support a safety signal for cardiac arrhythmias with linezolid at this time. However, the Division of Anti-infective and Ophthalmology Products has concerns about a potential signal based on data reviewed from a clinical trial submitted by the sponsor. They have requested a postmarketing study to assess the risk of QT prolongation, which is to be completed by the end of the third quarter of 2009.

No actions are recommended at this time, and we will continue routine monitoring for cardiac arrhythmias with the use of linezolid and await the results of the postmarketing study.

1 BACKGROUND

1.1 INTRODUCTION

Linezolid was brought to the Pediatric Advisory Committee (PAC) on November 16, 2006 for its one-year post-pediatric exclusivity review. At that time, six cardiac-related adverse event cases in the pediatric age group were noted (three reports of tachycardia, and single reports of chest pressure with an irregular heart beat, an abnormal electrocardiogram, and an unspecified arrhythmia). These cases, although temporally related, could not be definitively associated with linezolid as other factors may have been involved. The committee requested a report to assess any possible association of cardiac events with linezolid in both pediatrics and adults. A focused Office of Surveillance and Epidemiology (OSE) review, dated December 21, 2006, was conducted and no safety signals were found; data mining analysis did not find any association between linezolid and cardiac arrhythmias (see Appendix 1). There will be a 2-year follow-up report given to the PAC in November 2008. To address this 2-year follow-up, the Office of Pediatric Therapeutics (OPT) requested an updated Adverse Event Reporting System (AERS) search to identify if there have been any additional cardiac adverse events for adults and pediatrics for linezolid since the previous review. If this updated review duplicates the December 2006 findings, OPT anticipates that they will send the report to the PAC without further action.

1.2 CURRENT PRODUCT LABELING

Cardiac arrhythmias are not listed in the current labeling.

2 METHODS AND MATERIALS

For the December 2006 review, data mining and AERS searches were conducted with the MedDRA HLGT *Cardiac arrhythmias*. For this review, searches were conducted with the same MedDRA terms, but based on new information, an additional search was conducted with the HLT *ECG investigations* to capture any cases reported as electrocardiogram abnormalities. This additional search was conducted to include reports received from market approval (4/18/2000) through 5/31/2008.

2.1 DATA MINING

A data mining analysis was conducted on 6/9/2008 using WebVDME 6.0 with linezolid using the HGLT *Cardiac arrhythmias* and an EB05 > 1. (Typically, an EB05 ≥ 2 is used to identify potential signals; however, a search using an EB05 > 2 retrieved zero results.) An additional data mining analysis was conducted on 6/27/2008 with linezolid using the HLT *ECG investigations* and an EB05 > 1.

A data mining analysis attempts to identify disproportionate reporting between drugs and events based on the records contained in AERS and reports this disproportionality as an EB05 score. The higher the EB05 score, the higher the association between the drug and event, as reported in the database being analyzed. An elevated EB05 indicates that the drug-event pair in question had disproportionally more reports in the database than did

this event in association with other drugs in the database. **Note that the EB05 score measures relative reporting of various events among all drugs in the database and that an elevated EB05 does not automatically imply causality between the drug and event of interest.**[1, 2]

2.2 AERS SELECTION OF CASES

AERS was searched on 6/9/2008 using the existing product group for linezolid (AERS Search "Owner"—Ronald Wassel) and the HLGT *Cardiac arrhythmias* (MedDRA v.11.0) for cases with an FDA received date of 9/16/2006 (following the search dates of the previous review) through 5/31/2008, inclusive. AERS was also searched on 6/26/2008 with linezolid and the HLT *ECG investigations* for cases with an FDA received date of 4/18/2000 through 5/31/2008, inclusive.

3 RESULTS

3.1 DATA MINING

The data mining search found only one result for cardiac arrhythmias with an EB05 score of ≥ 1, which was for tachycardia with an EB05 score of 1.37 based on an N of 42 non-adjudicated cases (this compares to an EB05 score of 1.42 with an N of 36 in the 2006 review).

3.2 ADVERSE EVENT CASES

The AERS search retrieved 35 unduplicated cases that included the following preferred terms (PT) related to cardiac arrhythmias or electrocardiogram abnormalities:

- tachycardia 7
- arrhythmia 5
- atrial fibrillation 4
- electrocardiogram QT prolonged 4
- torsade de pointes 4
- electrocardiogram abnormal 3
- ventricular extrasystoles 3
- ventricular tachycardia 3
- bradycardia 2
- ventricular fibrillation 2
- atrioventricular block complete 1
- cardio-respiratory arrest 1
- electrocardiogram ST segment abnormal 1
- sick sinus syndrome 1
- supraventricular tachycardia 1
- ventricular arrhythmia 1

The total of these terms is greater than 35 as the cases may have included more than one term.

These 35 cases incorporated 21 foreign cases (Japan had the most with 11) and 14 domestic cases.

There were two pediatric cases; one from Belarus in a two–month–old male (tachycardia) and the other from Ireland in a 10–year–old female (abnormal electrocardiogram).

4 DISCUSSION/SUMMARY OF CASES

The December 2006 review (see Appendix 1) of cardiac arrhythmias in adults and pediatric patients retrieved 96 unduplicated cases, but the majority (73) were considered related to other causes, primarily serotonin syndrome. The 23 cases considered possibly related because of a temporal association 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. These cases were often lacking details 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 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 did not support a safety signal for cardiotoxicity with linezolid at the time of the review.

Of the 35 new cases in this update, 28 were assessed as unrelated, or not cases of a direct cardiotoxic effect of linezolid. These included:

- four cases of a drug interaction with serotonergic or adrenergic agents
- four cases attributed to the patients' underlying condition
- four cases in which the cardiac events mentioned in the narrative were not the primary reported adverse event for linezolid and were related to other causes
- three cases in which linezolid was continued without further recurrence of the events (negative rechallenge)
- two cases related to hypovolemia and/or metabolic abnormalities
- two cases miscoded as sudden death (which is a PT under the HLT *Ventricular arrhythmias and cardiac arrest*) because the narratives stated the patients died of unknown causes
- two cases coded as atrial fibrillation, which in fact were part of the patients' medical history

- a case of agitation/anxiety/toxic encephalopathy in an HIV patient with hepatitis C and cirrhosis (the patient exhibited tachycardia)
- a case reported as ST changes during surgery that improved spontaneously
- a case of a prolonged QTc interval that was only a short interval and thought to be due to a vibration in the bed and a loose ECG lead (patient experienced no further events).

Three of the cases of torsade de pointes (two foreign, one domestic) were most likely related to other drugs (fluconazole, fosfluconazole, and cibenzoline [a class I antiarrhythmic]). The fourth case of torsade de pointes (foreign) exhibited a negative dechallenge to linezolid in which the patient experienced new episodes after the drug was discontinued, so it is, therefore, considered unlikely related.

The remaining seven cases in this update, including the two pediatric cases, are discussed in greater detail below:

AERS CASE # 6269655; Pfizer Control # BY-PFIZER INC-2007019405 (Belarus)—A 2–month–old male born prematurely at 34 to 35 weeks gestation and with atrophic hydrocephaly was started on linezolid 10 mg/kg three times daily for treatment of sepsis. On the fourth day of treatment following the infusion, the patient developed **tachycardia** (heart rate 200-220 beats/min, up from 140-150 beats/min), hypotension (blood pressure 70/40 mmHg, down from 100/60 mmHg), and skin cyanosis. Linezolid was continued for an additional two days, but blood tests revealed leukopenia, acidosis, and an increased ALT and AST, at which point linezolid was discontinued. Subsequently, the physician learned that the solution of linezolid was administered more than 24 hours after first opening the bag. Following discontinuation, the adverse events resolved.

Reviewer's comment: Although there is a positive temporal relationship and a potential association with linezolid cannot be completely excluded, the patient's underlying condition (sepsis, possible shock with acidosis) could also be contributory. Also, there may have been a degradation reaction as storage recommendations are to keep the infusion bags in their foil laminate overwrap until ready to use to protect from light and moisture.

AERS CASE # 5851329; Pfizer Control # 2005102259 (Ireland)—A 10–year–old female receiving linezolid 600mg IV daily since [redacted] for methicillin–resistant *Staphylococcus aureus* (MRSA) pneumonia, developed hypokalaemia and was noted to have an **abnormal electrocardiogram** on [redacted]. It was reported that linezolid therapy was continued. Linezolid was discontinued on [redacted] and the patient recovered from the events at the time of the report. Concomitant medications included Tazocin (piperacillin/tazobactam), carbamazepine, Zoton (lansoprazole), Lamictal (lamotrigine) and clobazam.

Reviewer's comment: Although there is a positive temporal relationship and a potential association with linezolid cannot be completely excluded, hypokalemia could also be contributory to the cardiac event. In addition, linezolid was continued without further documentation of a continuing abnormal electrocardiogram.

AERS CASE # 6537000; Pfizer Control # GB-PFIZER INC-2008005639 (United Kingdom)—A 68–year–old male was treated with linezolid 600 mg IV for vancomycin-resistant enterococcal infection from [redacted] to [redacted]. The patient was receiving multiple other medications. In addition, the patient had a relapse of acute myeloid leukemia and received chemotherapy between [redacted] and [redacted] with fludarabine, cytarabine, and granulocyte-colony stimulating factor. On [redacted] the patient experienced sweating, vomiting, and increased heart rate (220 beats/min) and pulse. He was diagnosed with self-terminating **paroxysmal supraventricular tachycardia** and recovered from the events on the same day.

Reviewer's comment: Although there is a positive temporal relationship, causality cannot be assessed because of the multiple medications the patient was receiving. In addition, the event occurred one day after linezolid was stopped, and there were no other occurrences during the two weeks the patient was receiving the drug, suggesting an unlikely relationship.

AERS CASE # 6404421; Pfizer Control # DE-PFIZER INC-2007070733 (Germany)—A 74–year–old female with chronic obstructive pulmonary disease, acute respiratory failure, acute cholecystitis, and septicemia was treated with linezolid 1200 mg IV daily. The patient developed **ventricular tachycardia** from sinus rhythm persisting for five minutes. After injection of amiodarone 300 mg and potassium chloride 5 mmol, the event subsided without defibrillation. Concomitant medications included norepinephrine, dobutamine, amiodarone, unspecified diuretics, digoxin, and midazolam. The patient fully recovered.

Reviewer's comment: Although there is a positive temporal relationship, more likely explanations would include the patient's presumed cardiac dysfunction (based on drug therapy) and concomitant medications.

AERS CASE # 6594202; Pfizer Control # JP-PFIZER INC-2008024474 (Japan)—A 60–year–old male was hospitalized and underwent an unspecified operation by a cardiovascular surgeon. Originally, he was suspected of having an MRSA infection and was treated with vancomycin. As his renal function deteriorated, he was switched to teicoplanin. He was still in bad condition and MRSA was detected from sputum, pharynges, and nasal cavity. He was started on linezolid 1200 mg/day IV in late February 2008. The patient developed decreased platelets and **QT prolonged** on [redacted]. Linezolid was discontinued on 11Mar2008 and the patient is recovering.

Reviewer's comment: Although there is a positive temporal relationship between linezolid use and QT prolongation, and a potential association with linezolid cannot be completely excluded, there is scant information available to make an assessment. In addition, linezolid was continued without further documentation of continuing QT prolongation.

AERS CASE # 6329632; Pfizer Control # JP-PFIZER INC-2007045617 (Japan)—An 88–year–old male started to receive linezolid 1200 mg/day IV on 24May2007 for MRSA pneumonia. On [redacted], **QT prolonged** was observed on electrocardiogram. Linezolid was stopped and the patient recovered. The reporter classified the case as non-serious.

Reviewer's comment: Although there is a positive temporal relationship between linezolid use and QT prolongation, and a potential association with linezolid cannot be completely excluded, there is scant information available to make an assessment.

AERS CASE # 3915721; Pharmacia Control # 2003148797US (United States)—A 92–year–old male was in the intensive care unit of the hospital with **QT prolongation** after starting linezolid IV.

Reviewer's comment: Although there is a positive temporal relationship between linezolid use and QT prolongation, and a potential association with linezolid cannot be completely excluded, there is scant information available to make an assessment.

4.1 REVIEW DIVISION'S REQUEST FOR A POST-MARKETING STUDY

On June 20, 2008 the Division of Anti-infective and Ophthalmology Products sent an approval letter to Pfizer regarding their supplemental new drug applications providing for an amendment to the package insert with the information from the Phase 3 clinical trial A5951060 (M/1260/0080) "Linezolid vs. Vancomycin/Oxacillin/Dicloxacillin in the Treatment of Catheter-Related Gram-Positive Bloodstream Infections." Included in the letter was the following postmarketing requirement:

POSTMARKETING REQUIREMENTS UNDER 505(o)

Since Zyvox® (linezolid) was approved on April 18, 2000, for the treatment of adult patients with vancomycin-resistant *Enterococcus faecium* infections, nosocomial pneumonia, complicated and uncomplicated skin and skin structure infections, and community-acquired pneumonia, we have become aware of cases of fatal arrhythmias noted among patients who received Zyvox® (linezolid) in Study A5951060 that may be related to Zyvox® (linezolid) administration. This information was not available when Zyvox® (linezolid) was granted marketing authorization for the treatment of adult patients with vancomycin-resistant *Enterococcus faecium* infections, nosocomial pneumonia, complicated and

uncomplicated skin and skin structure infections, and community-acquired pneumonia. The cases of fatal arrhythmias in Study A5951060 are considered to be "new safety information" as defined in FDAAA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk, that is, the risk of fatal arrhythmia.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this signal of a serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess this signal of a serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct a clinical trial:

1. A clinical trial to assess the risk of QT prolongation.

The timetable you submitted on June 3, 2008 states that you will conduct this trial according to the following timetable:

Final Protocol Submission:	by December 31, 2008
Initiate (i.e. first subject dosed) and complete (i.e. last subject last visit) trial:	by March 31, 2009
Summary of Trial Results:	by July 31, 2009
Final Report Submission:	by September 30, 2009.

5 CONCLUSION

Consistent with the previous review, the available data from AERS and data mining do not support a safety signal for cardiac arrhythmias with linezolid at this time. There are cases with a temporal relationship, and thus a potential signal for QT prolongation; however, causality is not clear as other factors may be involved, or the information is too limited to make an assessment. The Review Division has concerns about a potential signal based on data reviewed from a clinical trial submitted by the sponsor. They have requested a postmarketing study to assess the risk of QT prolongation, which is to be completed by the end of the third quarter of 2009.

6 RECOMMENDATIONS

Based on the AERS data reviewed herein, no actions are recommended. We will continue routine monitoring for cardiac arrhythmias with the use of linezolid and await the results of the postmarketing study.

7 REFERENCES

1. Du Mouchel W, Pregibon D. Empirical bayes screening for multi-item associations. Proceedings of the conference on knowledge discovery and data; 2001 Aug 26-29; San Diego (CA): ACM Press: 67-76.
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.

APPENDIX 1

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINSTRATION	**DDRE POSTMARKETING SAFETY REVIEW**	
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	**FROM:** Ronald Wassel, Pharm.D. Safety Evaluator Division of Drug Risk Evaluation	**RCM # 2006-74** (PID # D060311) December 21, 2006
THROUGH: Rosemary Johann-Liang, M.D., Deputy Director for Mark Avigan, M.D., C.M., Director Division of Drug Risk Evaluation	**REQUESTOR/phone #:** Debbie Avant Reg Health Project Manager OND/PMHS 301-796-1642	
DRUG: Zyvox® (linezolid)		
THERAPEUTIC CLASSIFICATION: Oxazolidinone (synthetic antibiotic)	**NDA/IND:** # 21-130, 21-131, 21-132	**SPONSOR**: Pfizer
EVENT: Cardiac events (arrhythmias) in adult and pediatric patients		

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:

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cc: NDA # 21-130, 21-131, 21-132
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