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Center for Drug Evaluation and Research

Memorandum

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DATE: September 18, 2006

FROM: Sonny Saini, Pharm.D.
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THROUGH: Rosemary Johann-Liang, M.D., Deputy Director
for
Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation (DDRE)
Office of Surveillance and Epidemiology (OSE)

TO: Dianne Murphy, M.D., Director
Office of Pediatric Therapeutics (OPT)

SUBJECT: DDRE Postmarketing Safety Review:
Drug: Citalopram (Celexa®), NDAs #20-822, 21-046
Event(s): QT prolongation

*****Confidential: Contains Verispan Vector One® Data*****
Verispan Cleared for Pediatric Advisory Committee Meeting – November 2006

EXECUTIVE SUMMARY

This updated post-marketing safety review is in response to a request from Dr. Dianne Murphy (OPT) to search the AERS[1] database for new cases of QT prolongation temporally associated with citalopram (Celexa®) in pediatric patients, aged 16 years and younger. DDRE had previously analyzed reports of QT prolongation and citalopram in all age groups, as well as in pediatric patients as identified in a "One Year Post-Pediatric Exclusivity Postmarketing Adverse Events Review."[2,3] Information from the post-exclusivity pediatric review was presented at the

[1] Adverse Event Reporting System
[2] Phelan, K. Office of Drug Safety. ODS Post-Marketing Safety Review: Citalopram: QT Prolongation, Torsades de pointes, Ventricular Arrhythmias, Sudden death. Sept 30, 2002.

February 2004 Pediatric Advisory Committee (PAC) meeting, at which time members were informed that information on new reports would be provided at a future meeting. Consequently, information concerning citalopram and QT prolongation in pediatric patients presented in this document may be shared at the November 2006 PAC.

We searched the AERS database on August 3, 2006 for new reports of QT prolongation submitted from August 9, 2003 to August 3, 2006 that listed citalopram as a suspect agent for patients aged 16 years and younger. We retrieved and evaluated three unduplicated US cases that reported outcomes to include death (1), life-threatening (1), and a non-serious outcome (1). There were two male patients, aged 14 and 17 years old; and one female patient aged 12 years old. One case was prescribed citalopram for treatment of depression and anxiety; one case involved a patient that was not prescribed citalopram, but took an intentional overdose of a family member's citalopram; and the third case did not report the indication for citalopram use, but took an unspecified amount of citalopram concomitantly with an overdose of diphenhydramine, resulting in death.

Two cases described other confounding characteristics. In one, the patient was concomitantly taking atomoxetine, a drug documented in labeling to cause QT prolongation, and had a history of QT prolongation with antidepressant use. The second patient took a large overdose of diphenhydramine, a drug documented to cause QT prolongation.[4] The case that used citalopram at therapeutic doses reported a spontaneous[5] positive dechallenge when both citalopram and atomoxetine were discontinued, therefore making the role of citalopram in the development of the patient's QT prolongation unclear. However, citalopram may have played a role in the two cases of QT prolongation that occurred in the overdose cases, as there have been case reports of QT prolongation with citalopram overdose in the medical literature.[6]

The issue of QT prolongation associated with citalopram in all ages was previously reviewed by DDRE.[7] That review found a possible dose-dependent association between citalopram and QT interval prolongation that would be of clinical significance primarily in patients at risk for arrhythmia development regardless of age. However, this updated review of three new cases from August 9, 2003 to August 3, 2006 did not find any well-documented cases of QT prolongation associated with using regular doses of citalopram in pediatric patients. We must caution that the lack of a safety signal in this pediatric subgroup, based on the paucity of reports submitted, do not necessarily mean a lack of occurrence. DDRE will continue to monitor the AERS database for these events. As stated in labeling, animal studies with citalopram showed QT prolongation resulting in sudden death. Further, cases of QT prolongation with citalopram overdose are cited in the literature and reported to AERS We recommend that clinical

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[3] Phelan, K. Office of Drug Safety. ODS One Year Post-Pediatric Exclusivity Postmarketing Adverse Event Review: Citalopram. Sept 22, 2003.

[4] Sype JW, Khan IA. Prolonged QT interval with markedly abnormal ventricular repolarization in diphenhydramine overdose. *Int J Cardiol.* 2005; 99(2):333-335.

[5] Spontaneous dechallenge defined as discontinuation of active drug product without additional medical intervention

[6] Catalano G, Catalano MC, Epstein MA, et al. QTc interval prolongation associated with citalopram overdose: a case report and literature review. Clin Neuropharmacol. 2001 May-Jun;24(3):158-62.

[7] Phelan, K. Office of Drug Safety. ODS Post-Marketing Safety Review: Citalopram: QT Prolongation, Torsades de pointes, Ventricular Arrhythmias, Sudden death. Sept 30, 2002., DFS under NDA 20-822

pharmacology (thorough QT studies) evaluations be performed to clearly delineate QT effects of citalopram at therapeutic doses in order to more completely characterize this safety concern.

INTRODUCTION

OPT has asked DDRE to review new cases of QT prolongation in pediatric patients temporally associated with the use of citalopram submitted to the AERS database since August 9, 2003. A post-pediatric exclusivity adverse event review on citalopram was completed by DDRE on September 22, 2003 and reviewed pediatric citalopram cases during the first year following pediatric exclusivity approval (July 9, 2002 – August 9, 2003). This review found 42 unduplicated pediatric (0 – 16 years) adverse event cases during the first year following pediatric exclusivity approval for citalopram. Two of these 42 cases involved cardiovascular events. One case was an 8-year-old male experiencing three prolonged episodes of paroxysmal supraventricular tachycardia while on citalopram; and the second case was a 13-year-old female who experienced syncope and possible seizures. In addition, the issue of QT prolongation with citalopram in all ages was reviewed by DDRE in September 2002 in a review completed by Kathleen Phelan, R.Ph. (Safety Evaluator, DDRE) on September 30, 2002. This review found a possible dose-dependent association between citalopram and QT interval prolongation that would be of clinical significance primarily in patients at risk for arrhythmia development regardless of age.

DRUG INFORMATION AND LABELING

Citalopram, a highly selective serotonin reuptake inhibitor for oral administration, was approved as Celexa® on July 17, 1998 for the treatment of depression.

Currently citalopram is labeled for QT prolongation and torsades de pointes as follows:

> Other Events Observed During the Non-U.S. Postmarketing Evaluation of Celexa – ventricular arrhythmia, QT prolonged, torsades de pointes
>
> Overdosage: Human Experience – In more rare cases, observed symptoms included…ECG changes (including QTc prolongation, nodal rhythm, ventricular arrhythmia, and one possible case of torsades de pointes).

Additionally, the product labeling details in the Animal Toxicology section that a metabolite of citalopram, DDCT[8] caused QT prolongation (a known risk factor for sudden death) in beagle dogs.[9] Five of ten dogs died suddenly between weeks 17 and 31 after initiation of citalopram. QT prolongation occurred in dogs at doses producing DDCT plasma levels of 810 to 3250 nM (39-155 times the mean steady state DDCT level measured at the maximum recommended human daily dose of 60mg).

[8] Didemethylcitalopram, DDCT is not the principal metabolite of citalopram

[9] The dogs received doses of 8mg/kg/day, (4 times the maximum recommended daily human dose of 60mg on a mg/m^2 basis

In dogs, peak DDCT plasma concentrations are approximately equal to peak CT[10] plasma concentrations, whereas in humans, steady state DDCT plasma concentrations are less than 10% of steady state CT plasma concentrations. Assays of DDCT plasma concentrations in 2,020 citalopram-treated individuals demonstrated that DDCT levels rarely exceeded 70 nM; the highest measured level of DDCT in human overdose was 138 nM. While DDCT is ordinarily present in humans at lower levels than in dogs, it is unknown whether there are individuals who may achieve higher DDCT levels. The possibility that DCT[11] (the principal metabolite in humans) may prolong the QT interval in dogs has not been directly examined because DCT is rapidly converted to DDCT in that species.

DRUG USE

This information is provided by Verispan Vector One and is not to be used outside the FDA without prior clearance by Verispan obtained through the Office of Surveillance and Epidemiology.

The estimated total number of citalopram prescriptions (new and refill) dispensed by retail pharmacies (chain, independent, food stores, mass merchandisers) in the U.S. between January 2002 through June 2006 from Verispan Vector One® is 62,782,025.

From January 2002 through June 2006, 3.3% of the total market of citalopram was for pediatric patients (0 – 16 years). During this time period a total of 2,043,531 citalopram prescriptions were filled for pediatric patients. Each year from 2002 to 2006 the number of citalopram prescriptions steadily decreased for all ages and for pediatric patients. This is likely due to the introduction of Lexapro® (escitalopram) to the market by Forest Labs. Celexa's patent expired in late 2005, however Forest Labs began heavily marketing Lexapro (approved on August 14, 2002) in anticipation of the patent expiration for Celexa.

Table 1 – Drug Usage for citalopram

	Total Rxs (1/2002 – 6/2006)	Total Rxs 2002	Total Rxs 2003	Total Rxs 2004	Total Rxs 2005	Total Rxs 2006*
Total Market	62,782,025	19,894,618	15,649,940	11,278,620	10,160,773	5,798,074
0-16 years	2,043,531	672,792	556,164	383,174	282,659	148,742
17+ years	60,364,883	19,133,960	15,025,011	10,801,697	9,788,301	5,615,914
Unspecified	373,611	87,866	68,765	93,749	89,813	33,418

(Numbers are absolute, do not add zeros)
*Through 2nd quarter year 2006

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 1.8 billion prescription claims, representing over 150 million unique patients.

[10] citalopram
[11] Demethylcitalopram, DCT is the principal metabolite of citalopram

The number of dispensed prescriptions is obtained from a sample of virtually all retail pharmacies throughout the U.S. and represents approximately half of the retail prescriptions dispensed nationwide. Verispan receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

LITERATURE SUMMARY

A PUBMED search of the English-language literature with reference to human pediatric patients did not identify any reports of QT prolongation associated with the use of citalopram in children. However, a PUBMED search of the English-language with reference to human patients of any age and QT prolongation associated with the use of citalopram identified five published articles. One observational study found that although there was no significant prolongation of the QT interval following monotherapy of an antipsychotic agent (haloperidol, olanzapine, risperidone, quetiapine, or clozapine); a combination of these drugs with antidepressants (citalopram, escitalopram, sertraline, paroxetine, fluvoxamine, mirtazapine, venlafaxine, or clomipramine) caused a significant QT prolongation.[12] Other articles detailed the occurrence of QT prolongation with overdose of citalopram.[13]

SELECTION AND SUMMARY OF CASES

On August 3, 2006, we searched the AERS database for cases of QT prolongation temporally associated with the use of citalopram. We used the following MedDRA terms and search levels:

Electrocardiogram QT corrected interval prolonged (PT)
Electrocardiogram QT prolonged (PT)
Death (PT)
Sudden death (PT)
Ventricular arrhythmias and cardiac arrest (HLT) –
PT terms under this HLT: accelerated idioventricular rhythm, cardiac arrest, cardiac arrest neonatal, cardiac death, cardiac fibrillation, cardio-respiratory arrest, cardio-respiratory arrest neonatal, electromechanical dissociation, parasystole, rhythm idioventricular, sudden cardiac death, sudden death, torsade de pointes, ventricular arrhythmia, ventricular asystole, ventricular extrasystoles, ventricular fibrillation, ventricular flutter, ventricular pre-excitation, ventricular tachyarrhythmia, ventricular tachycardia

Of 569 reports of adverse events for citalopram in pediatric patients aged 0 to 16 years old, we found 10 reports of citalopram temporally associated with QT prolongation in the AERS database, of which we excluded 7. The excluded reports included duplicates (1), patients not on citalopram (2), normal QT complex (1), and suicide reports not involving QT prolongation (3).

[12] Sala M, Vicentini A, Brambilla P, et al. QT interval prolongation related to psychoactive drug treatment: a comparison of monotherapy versus polytherapy. *Ann Gen Psychiatry.* 2005;4(1).
[13] Catalano G, Catalano MC, Epstein MA, et al. QTc interval prolongation associated with citalopram overdose: a case report and literature review. Clin Neuropharmacol. 2001 May-Jun;24(3):158-62.

Confounding: We reviewed three AERS cases of QT prolongation associated with citalopram. Of the three cases, two were confounded. One case was confounded because the patient was concomitantly taking atomoxetine, a drug documented in labeling to cause QT prolongation, and had a history of QT prolongation with paroxetine and imipramine combination therapy; and the second case was confounded because the patient took an overdose of diphenhydramine, a drug documented to cause QT prolongation.[14]

Summary of Cases (n=3)

ISR #4913054; USA; February 2006, Death
A literature[15,15] report from the US describes an outcome of death in a 12-year old female who concomitantly took an unknown amount of citalopram and 4 to 5 grams of diphenhydramine. The indication, dates of therapy, and dosage of citalopram were not reported. The patient presented to the Emergency Room (ER) for treatment due to altered mental status. While in the ER the patient's condition continued to worsen and the patient developed cardiac events, including bradycardia, a wide complex rhythm on ECG, and cardiac arrest. The patient died after being diagnosed with brain death, and after withdrawal of care. There was no medical history reported.

Reviewer's comment: This case is confounded because the patient had a large overdose of diphenhydramine, a drug documented to cause QT prolongation during overdose.[14]

ISR #4294234; USA; February 2004, Hospitalized
A 17-year-old African-American male developed seizures, intermittent tachyarrhythmias, wide QRS complex rhythms on ECG, and sinus tachycardia while taking an intentional overdose (2400 mg) of citalopram that was prescribed for another family member. The onset of the adverse events after taking the citalopram overdose was not reported. The patient was hospitalized and experienced two seizures which resolved with lorazepam. The patient's medical history included a prior history of marijuana use and asthma. Concomitant medications were not provided.

Reviewer's comment: The normal dose of citalopram is 20-40 mg daily. This case did involve an intentional overdose, and represents a possible association of citalopram and QT prolongation in overdose.

ISR #4379303; USA; June 2004, Other
A 14-year-old male developed QT prolongation while taking citalopram 40 mg daily for depression and anxiety. Six months after the initiation of citalopram a cardiologist diagnosed the patient with QT prolongation. An ECG documented the QT_C to be 445 msec (baseline unknown). Citalopram and atomoxetine were immediately discontinued and a repeat ECG documented resolution at QT_C 408 msec. There was no rechallenge. The patient's medical

[14] Sype JW, Khan IA. Prolonged QT interval with markedly abnormal ventricular repolarization in diphenhydramine overdose. *Int J Cardiol.* 2005; 99(2):333-335.
[15] Sype JW, Khan IA. Prolonged QT interval with markedly abnormal ventricular repolarization in diphenhydramine overdose. *Int J Cardiol.* 2005; 99(2):333-335.
[15] This literature report was located in the AERS database, but was not found in PUBMED.

history included QT prolongation associated with previous paroxetine and imipramine combination therapy and history of attention deficit disorder. Concomitant medication included atomoxetine.

Reviewer's comment: This case is confounded because the patient concomitantly took atomoxetine, which is labeled in the post-marketing section for rare occurrences of QT prolongation.[16] Additionally, this case may have an additional potential confounder because the patient had a prior history of QT prolongation while on paroxetine and imipramine combination therapy. The role of citalopram or atomoxetine cannot be excluded from this patient's documented QT prolongation.

CONCLUSIONS/RECOMMENDATIONS

We queried the AERS database for new pediatric cases of citalopram associated QT prolongation reported to the Agency since August 9, 2003. We found three new cases. The three cases were domestic and were reported in children aged 12, 14 and 17 years old. Although, the 17 year old case does not meet the search criteria based on children aged 16 years old and younger, we include the case in this review based on the request of OPT.

The three new pediatric cases reported QT prolongation possibly as a consequence of citalopram use. In two of the three cases QT prolongation was reported after overdose; with one of the overdoses involving an unspecified amount of citalopram and 4 to 5 grams of diphenhydramine. The second overdose was intentional and involved ingesting 2.4 grams of citalopram. The third QT prolongation case involved a child on normal doses of citalopram (40mg daily for depression and anxiety) who concomitantly took atomoxetine. This third case is confounded with the concomitant use of atomoxetine, which is labeled for QT prolongation; as well as is confounded with a previous history of QT prolongation with other antidepressants.

The cases reported death (1- citalopram and diphenhydramine overdose), life-threatening (1- intentional overdose), and a non-serious outcome. The case with the non-serious outcome reported a positive spontaneous dechallenge response (without additional medical intervention) when citalopram and atomoxetine were immediately discontinued. The role of citalopram in the development of this patient's QT prolongation during normal use is unclear because of the concomitant use and simultaneous discontinuation of atomoxetine. However, citalopram may have played a role in the two cases of QT prolongation occurring in the overdose setting, as there have been case reports of QT prolongation with citalopram overdose in the medical literature.[17]

The issue of QT prolongation with citalopram in all ages was previously reviewed by DDRE. [18] That review found a possible dose-dependent association between citalopram and QT interval prolongation that would be of clinical significance primarily in patients at risk for arrhythmia development regardless of age. However, this updated review of three new cases from August 9,

[16] Strattera Product Label. January 10, 2006. Eli Lilly and Company

[17] Catalano G, Catalano MC, Epstein MA, et al. QTc interval prolongation associated with citalopram overdose: a case report and literature review. Clin Neuropharmacol. 2001 May-Jun;24(3):158-62.

[18] Phelan, K. Office of Drug Safety. ODS Post-Marketing Safety Review: Citalopram: QT Prolongation, Torsades de pointes, Ventricular Arrhythmias, Sudden death. Sept 30, 2002., DFS under NDA 20-822

2003 to August 3, 2006 did not find any well-documented cases of QT prolongation associated with using regular doses of citalopram in pediatric patients. We must caution that the lack of a safety signal in this pediatric subgroup, based on the paucity of reports submitted, do not necessarily mean a lack of occurrence. DDRE will continue to monitor the AERS database for these events. As stated in labeling, animal studies with citalopram showed QT prolongation resulting in sudden death. Further, cases of QT prolongation with citalopram overdose are cited in the literature and reported to AERS We recommend that clinical pharmacology (thorough QT studies) evaluations be performed to clearly delineate QT effects of citalopram at therapeutic doses in order to more completely characterize this safety concern.

Sonny Saini, Pharm.D. signed 09/18/06
Safety Evaluator

Concur:

Marilyn R. Pitts, Pharm.D. signed 09/18/2006

This document was previously signed-off in DFS on September 18, 2006
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