

MEMORANDUM

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

DATE: September 22, 2003

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THROUGH: Mark Avigan, M.D., Acting Director  
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TO: Solomon Iyasu, MD, MPH., Team Leader  
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Office of Counter-Terrorism and Pediatric Drug Development, HFD-950

SUBJECT: One Year Post-Pediatric Exclusivity Postmarketing Adverse Event  
Review  
Drug : Citalopram (Celexa®) NDA# 20-822, 21-046  
Pediatric Exclusivity Approval Date: 9 July 2002

**Executive Summary**

The AERS database was searched for reports of adverse events associated with citalopram in patients aged 0 through 16 years that were received by the FDA during the first year following pediatric exclusivity approval. Forty-two unduplicated pediatric adverse event cases were found. Sixteen cases involved *in utero* exposure and 26 cases involved direct ingestion of citalopram.

Adverse events in the *in utero* cases are all unlabeled because citalopram labeling includes no human data regarding use in pregnancy. No pattern of adverse effects emerges from these cases to suggest a drug-related effect on development. Previous ODS reviews examined congenital eye malformations with citalopram and neonatal withdrawal syndrome after maternal use of SSRI antidepressants.

Adverse events in the 26 direct ingestion cases are either labeled, related to labeled events, or attributable to drugs other than citalopram. There was no difference noted between pediatric and adult adverse event profiles based on the top 20 reported adverse event terms.

We will continue monitoring citalopram adverse effects in children.

**AERS Search Results: Citalopram**

Pediatric reports were searched from age 0 to 16 to show all reports in pediatric patients. Pediatric reports were searched from age 2 to 16 to provide an estimate of reports occurring as a result of direct citalopram ingestion by pediatric patients and to eliminate adverse event reports resulting from *in utero* exposure, which represent a significant portion of reports.

AERS Search including all sources - U.S. & foreign

**A. From marketing approval date (17 July 1998) through 1-year post-exclusivity approval (9 August, 2003).**

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

	All reports (US)	Serious(US)	Death(US)
All ages	6432 (5086)	2644 (1478)	503 (248)
Adults (≥17)	4627 (3522)	2189 (1204)	437 (219)
Peds (0-16)	193 (136)	117 (61)	5 (0)
Peds (2-16)	133 (122)	60 (50)	0 (0)

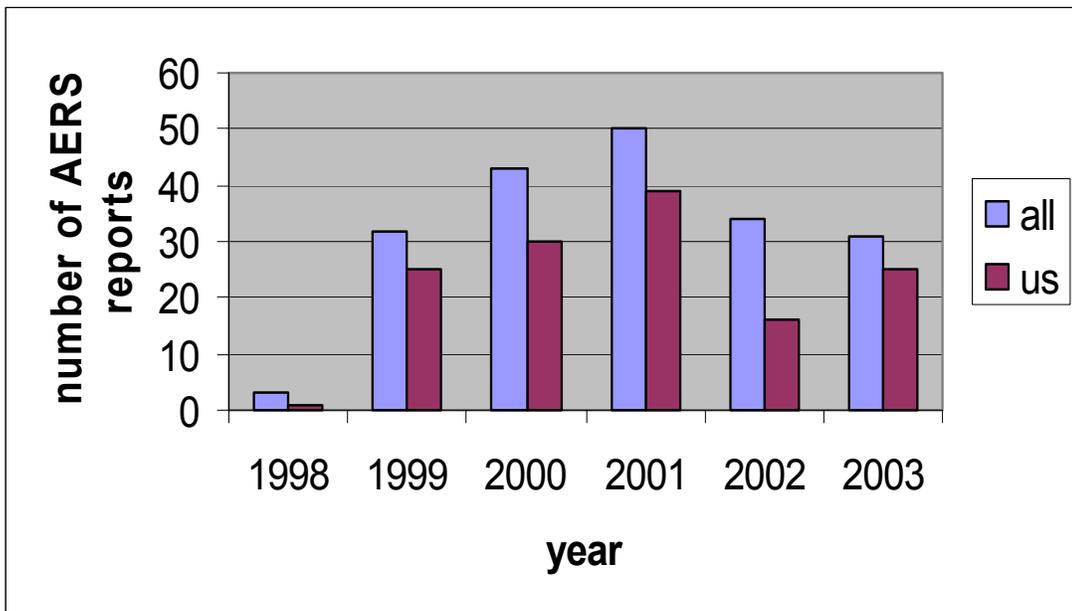


Figure 1: Reporting trend for pediatric reports (age 0 – 16 years) from approval date (17 July 1998)

- Counts of top 20 reported event preferred terms for all ages, adults, and pediatric age groups since drug approval. Events not previously described in the label are underlined.

*All ages:* nausea (414), dizziness (312), asthenia (304), headache (293), sedation (269), tremor (268), insomnia (266), sweating increased (231), convulsions (204), diarrhea (204), drug interaction (200), anxiety (195), confusional state (188), hyponatremia (186), vomiting (177), depression (176), dermatitis (172), agitation (171), completed suicide (161), paresthesia (154)

*Adults:* nausea (353), dizziness (263), asthenia (262), headache (245), insomnia (232), tremor (215), sedation (210), sweating increased (191), diarrhea (179), drug interaction (170), confusional state (166), anxiety (163), convulsions (155), hyponatremia (152), vomiting (148), depression (147), completed suicide (144), agitation (142), paresthesia (131), condition aggravated (112)

*Peds aged 0 to 16:* complications of maternal exposure to therapeutic drugs (33), maternal drugs affecting fetus (23), convulsions (13), neonatal disorder nos (12), apgar score low (11), hypertonia (9), pregnancy (9), dyspnea (8), premature baby (8), tremor (8), vomiting (8), depression (7), muscle twitching (7), nausea (7), aggression (6), Caesarean section (6), dizziness (6), drug withdrawal syndrome neonatal (6), overdose (6), amenorrhea (5)

*Peds aged 2 to 16:* convulsions (9), depression (7), tremor (7), vomiting (7), aggression (6), dizziness (6), muscle twitching (6), nausea (6), overdose (6), amenorrhea (5), chest pain (5), condition aggravated (5), dyspnea (5), dystonia (5), headache (5), hypertonia (5), insomnia (5), syncope (5), weight increased (5), agitation (4)

**B. From Pediatric Exclusivity approval date (9 July 2002) through AERS data cut-off date (9 August 2003):**

- Counts of reports: Table 2

	All reports (US)	Serious (US)	Death (US)
All ages	962 (586)	898 (539)	167 (92)
Adults (≥17)	791 (475)	752 (447)	140 (82)
Peds (0-16)	54 (36)	49 (31)	2 (0)
Peds (2-16)	34 (31)	29 (26)	0 (0)

- Counts of top 20 reported event preferred terms for all ages, adults, and pediatric age groups since pediatric exclusivity approval date (9 July 2002). Events not previously described in the label are underlined.

*All ages:* completed suicide (63), drug interaction (57), convulsions (53), fall (47), dizziness (46), nausea (44), hyponatremia (43), overdose (42), confusional state (41), depression (41), tremor (41), maternal drugs affecting fetus (39), drug toxicity (37), loss

of consciousness (34), somnolence (34), vomiting (34), agitation (32), drug withdrawal syndrome (30), grand mal convulsion (30), headache (29)

*Adults:* completed suicide (55), drug interaction (53), fall (43), convulsions (42), nausea (42), hyponatremia (40), dizziness (39), depression (38), tremor (38), confusional state (37), overdose (34), loss of consciousness (31), somnolence (31), vomiting (31), agitation (29), drug toxicity nos (27), grand mal convulsion (27), asthenia (26), drug withdrawal syndrome (25), anxiety (24)

*Peds aged 0 to 16:* maternal drugs affecting fetus (18), convulsions (7), aggression (4), neonatal disorder nos (4), suicidal ideation (4), apgar score low (3), congenital abnormality nos (3), markedly reduced dietary intake (3), weight increased (3), abnormal behavior nos (2), Caesarian section (2), complications of maternal exposure to therapeutic drugs (2), condition aggravated (2), conversion disorder (2), diarrhea (2), drug interaction (2), dyspnea (2), dystonia (2), electrocardiogram Qt corrected interval prolonged (2), fall (2)

*Peds aged 2 to 16:* convulsions (6), aggression (4), suicidal ideation (4), markedly reduced dietary intake (3), weight increased (3), abnormal behavior nos (2), condition aggravated (2), conversion disorder (2), diarrhea (2), drug interaction nos (2), dyspnea (2), dystonia (2), electrocardiogram Qt corrected interval prolonged (2), fall (2), headache (2), insomnia (2), medication error (2), overdose (2), pain nos (2), paresthesia (2)

**Postmarketing review of all peds adverse event reports received during the 1 year after pediatric market exclusivity was granted.**

**A. Characteristics of pediatric (aged 0 to 16 years) reports.**

Of 54 reports, 4 were duplicates, 7 were for escitalopram, one involved an adult. Of the remaining 42 cases, 16 were *in utero* exposure and 26 were direct ingestions by child.

Pediatric patients exposed to citalopram in utero (16):

*Gender:* 2 female, 11 male, 3 unknown

*Standard AERS age breakdown:*

0-<1 mo.	12
1 mo.- <2 yrs	3
2-5 yrs	1

*Serious Outcomes:* 1 death, 7 congenital anomalies, 4 hospitalizations, 1 life threatening, 3 medically important events

Pediatric patients exposed to citalopram by ingestion (26):

*Gender:* 9 female, 17 male

*Standard AERS age breakdown:*

0-<1 mo.	0
1 mo.-<2 yrs	1
2-5 yrs	1
6-11 yrs	9
12-16 yrs	15

*Serious Outcomes:* 0 death, 10 hospitalizations, 4 life threatening, 2 disability, 3 required intervention, 7 medically important events

*Indications for citalopram use:*

6 unknown

2 ingestion of another person's prescription

13 depression

1 each of the following indications – anxiety/panic disorder, generalized anxiety disorder, post-traumatic stress disorder, anxiety/aggression, oppositional-defiant disorder

*Doses:*

range (N=20): 5 to 60 mg/day

mean: 20.5 mg/day; median: 20 mg/day

4 unknown

2 overdose ingestions of another person's citalopram prescription

**B. Comments regarding labeling status of the top 20 pediatric adverse events and comparison with adult adverse event profile.**

Current citalopram labeling includes no human data on effects of use during pregnancy. Labeling states, "There are no adequate and well-controlled studies in pregnant women; therefore, citalopram should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus." Similarly, there is no labeled information specific to pediatric use. Labeling states, "Safety and effectiveness in pediatric patients have not been established."

The top 20 reported adverse events in pediatric patients aged 0 to 16 years include 12 that are not labeled. Six of the 12 unlabeled adverse events refer to *in utero* exposure. Five of these six terms are vague or refer to the mother. They are maternal drugs affecting fetus, neonatal disorder nos, congenital abnormality nos, Caesarian section, and complications of maternal exposure to therapeutic drugs. The one specific unlabeled term is apgar score low. The remaining six unlabeled terms also appear in the pediatric reports in patients aged 2 to 16 years and are discussed below.

When reports are limited to an age range of 2 to 16 years to minimize *in utero* exposure reports, the profile provided by the top 20 reported adverse events changes to include medication error, overdose, headache, insomnia, pain, and paresthesias. The top 20 adverse events reported in 2 to 16 year olds do not include any events that are specific, unlabeled, and related to citalopram use. Although nine of the events are not labeled, three of these are related to labeled events: suicidal ideation is implied by suicide attempt; headache is implied by migraine; markedly reduced dietary intake is implied by weight decrease. Four others of the nine unlabeled events are nonspecific and difficult to assess for labeling: abnormal behavior nos, condition aggravated, medication error, and pain. Conversion disorder and fall are the only unlabeled adverse events that are both specific and not similar to a labeled term. Review of the cases reveals that the conversion disorders are associated with paroxetine and escitalopram use and the two falls are associated with convulsion, a labeled event. Thus, all 20 most frequently reported adverse events that are possibly related to citalopram use in 2 to 16 year old patients are labeled or related to labeled events.

Overall, the profiles of the top 20 adverse events in children aged 0 to 16 and 2 to 16 do not differ from that of adults aged 17 and over except for those related to *in utero* citalopram exposure.

### **C. Comments and analyses of pediatric events not recognized for adult population.**

The adverse events in the 16 *in utero* citalopram exposure cases are all unlabeled, since labeling does not include human data on use in pregnancy. The seven reported congenital anomalies are possible congenital megacolon (1), congenital ptosis, eye muscle paresis, and nystagmus (1), cleft lip and no nose (1), incomplete kidney and physiologically immature hip (1), heart murmur and renal dysgenesis (1), club foot and kidney located lower in pelvis than normal (1), patent ductus arteriosus and patent foramen ovale (1).

The issue of congenital eye malformations with citalopram *in utero* exposure was evaluated by ODS in March 2003. That review found more cases of congenital eye malformation with citalopram than with other antidepressant drugs, but the number of cases was small, the malformations were varied and a firm conclusion could not be drawn. That review is available in DFS under NDA 20-822.

This review reveals three cases of congenital kidney effects. The reported adverse effects vary so no pattern is apparent.

The adverse events reported in the remaining nine *in utero* citalopram exposure cases are

- hypoxia, hypotonia, difficulty feeding in a premature infant
- respiratory problems, hypotonia, hypertonia, tremors in a male neonate
- fetal asphyxia during birth induced due to pre-eclampsia
- myoclonus and ear infection in a male neonate
- delayed head control at age 1 month in a male infant
- CNS irritability, limb spasms, chills in a male neonate

- catatonia, abnormal movements, shallow breathing in male neonate with *in utero* cocaine exposure
- withdrawal syndrome in a 2-day-old male
- sudden infant death of a 4-month-old male.

The issue of neonatal withdrawal syndrome after *in utero* exposure to SSRI antidepressants was reviewed by ODS in November 2001. That review recommended addition of neonatal withdrawal syndrome to SSRI labeling. The labeling changes are being drafted by HFD-120. That review is available in DFS under NDA 20-822.

Of the 26 cases of citalopram ingestion by pediatric patients, 8 cases include unlabeled adverse events possibly related to citalopram use and are described below. Three additional cases described below include labeled events of sufficient severity to warrant mention. Unlabeled events are underlined.

#### General events

- One case reports that crushed citalopram yields a positive cocaine reaction in a police drug field test kit. The adverse event was trauma caused by police arrest of a 14-year-old female and was not caused by citalopram ingestion.

#### Cardiovascular events

- Three prolonged (10-minutes) episodes of paroxysmal supraventricular tachycardia that were not relieved by the valsalva maneuver occurred in an 8-year-old boy after 5 days of citalopram treatment for depressive disorder. Previously, the child experienced rare 2-minute episodes of paroxysmal ventricular tachycardia that were easily treated by valsalva maneuvers. Electrolytes were normal. The event resolved with discontinuation of citalopram and did not recur when citalopram was restarted at a reduced dosage.
- A 13-year-old female experienced syncope and possible seizure the same day her citalopram dosage was increased from ½ to a full tablet of unknown strength for an unknown indication. She was found to have a borderline prolonged corrected QT interval. Other tests were normal. After discontinuation of citalopram, no syncope or seizures occurred and cardiac follow-up found ECG to be normal. She was also being treated for asthma.

The issue of QT prolongation with citalopram in all ages was reviewed by ODS in September 2002. 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. That review is in DFS under NDA 20-822.

#### Neurological events

- A 13-year-old male experienced demyelinating spinal cord lesions while taking citalopram 20 mg per day for depression. Symptoms of weakness and numbness began after about 2 weeks of citalopram treatment and progressed to absence of all motor function below the shoulder level. No etiology has been determined and

citalopram treatment continues. The physician does not believe citalopram is related to the event.

#### Special senses events

- A 15-year-old female developed a loss of peripheral visual fields while taking citalopram 20 mg per day for depression and Depo Provera for contraception. Peripheral vision improved after Depo Provera was discontinued. Citalopram treatment continues.
- A 10-year-old male was diagnosed with posterior subcapsular cataracts and visual changes after about 18 months taking citalopram 10 mg per day to treat anxiety and aggression. He had been taking risperidone for about 13 months at cataract diagnosis.

The serious adverse effects of demyelinating spinal cord lesions, loss of peripheral visual fields, and cataracts cannot be confidently attributed to citalopram because of complexity of effects, irreversibility of some effects, and concomitant drugs used. However, an association cannot be excluded. Continued monitoring of these issues is recommended.

#### Psychiatric events

- A 15-year-old male experienced violent behavior, impaired memory, severe depression, and abrupt mood swings during the 2 weeks he received citalopram to treat depression. The events resolved when citalopram was stopped.
- A 13-year-old male experienced violent behavior, aggression, anger, suicidality, and argumentativeness during use of citalopram and, some time previously, during use of paroxetine to treat depression. He did not display these behaviors when not on antidepressants.
- An 8-year-old male experienced cognitive impairment, aggressive behavior, difficulty sleeping, and paresthesia starting 1 month after citalopram 10 mg per day was started for oppositional-defiant disorder. The events resolved when citalopram was stopped.
- An 8-year-old male developed agitation with psychomotor instability, manic reaction, delusions, and attention disorders 2 weeks after initiation of citalopram 20 mg per day to treat depression. He was receiving no other medications. The events did not resolve when citalopram was discontinued but required treatment with risperidone. He has a history of depression with aggressiveness, anguish, tics, and persecution.
- A 10-year-old female receiving multiple medications for multiple health problems displayed suicidal and homicidal behaviors beginning in the same month that citalopram 60 mg per day was initiated for depression. Specific dates are not provided. The events resolved when citalopram was stopped.

The adverse events reported in the remaining 15 citalopram ingestion cases are

- adverse events temporal to concomitant medications or disease (7)
- overdose (3) with QT prolongation (1), tachycardia (1), seizure (1)
- serotonin syndrome (2)
- increased seizure frequency attributed to disruption of ketogenic diet by sorbitol in Celexa oral solution (1)
- convulsion, dizziness, headache, and double vision (1)
- syncope (1)

**D. Comments and analyses of events uniquely identified in pediatric population, including increased frequency of any expected events.**

*In utero* adverse effects are difficult to assess because of difficulty in determining population exposure and because of the high background rate of congenital anomalies. Patterns of anomalies occurring with a particular drug or drug class may indicate a causal association. There are no clear patterns in the congenital anomalies in this review. Continued monitoring of the effects of citalopram use during pregnancy is recommended.

This review identified no adverse events unique to pediatric patients. However, because of the recent study showing increased suicidality in pediatric patients receiving paroxetine to treat depressive disorder, clinical trial data for the SSRI drug class, including citalopram, was examined in ODS for suicide-related adverse events. Follow-up analysis is planned after which the need for further study or action can be determined. The review of suicidality in pediatric clinical trials with paroxetine and other antidepressant drugs, authored by Andrew Mosholder, Epidemiologist, is in DFS under NDA 20-031.

**E. Summary and comment on death reports.**

The single death report received during the first year after pediatric exclusivity approval is sudden infant death of a 4-month-old male who had been exposed to citalopram *in utero*. Autopsy revealed no cause of death. No conclusions can be drawn from this single case.

**F. Summary of all pediatric reports during period.**

Forty-two unique reports in patients aged 0 to 16 consist of 16 *in utero* and 26 direct ingestion exposures. Two direct ingestions were overdoses of another person's prescription. Among the *in utero* exposure cases, seven report a congenital anomaly. There is no consistent pattern among the anomalies, although three involve the kidneys. The other reported effects of *in utero* exposure, such as respiratory problems and tremor, can have multiple causes in the neonate and are difficult to attribute to drug. The one death case reported sudden infant death in a 4-month-old exposed to citalopram *in utero*. An association with citalopram cannot be confirmed or excluded. There is one case each of withdrawal syndrome and eye problems. Both issues have been reviewed by ODS.

The 26 direct ingestion cases mainly report adverse events that are similar to those seen in adults and in labeling. These comprise cardiovascular and nervous system events. Two reported adverse events not labeled or reported in adults are demyelinating spinal cord lesions and loss of peripheral visual fields. In both cases, citalopram use continues and association of the adverse event with citalopram cannot be confirmed or excluded. QT prolongation with citalopram has been reviewed by ODS and was found to be possibly related to dose in all aged patients. Suicidality in children taking SSRIs was recently reviewed by ODS and additional study of the issue is planned.

## **Summary**

Forty-two unduplicated pediatric adverse event cases were reported for citalopram during the first year of pediatric exclusivity. Sixteen cases involved *in utero* exposure and 26 cases involved direct ingestion of citalopram.

Adverse events in the *in utero* cases are all unlabeled because citalopram labeling includes no human data regarding use in pregnancy. No pattern of adverse effects emerges from these cases to suggest a drug-related effect on development. Previous ODS reviews examined congenital eye malformations with citalopram and neonatal withdrawal syndrome after maternal use of SSRI antidepressants.

Adverse events in the 26 direct ingestion cases are either labeled, related to labeled events, or attributable to drugs other than citalopram. Because of a recent study finding increased suicidality in pediatric patients receiving paroxetine to treat depression, an initial review of suicidality in pediatric clinical trials with paroxetine and other antidepressant drugs, including citalopram, has recently been completed by ODS, with a follow-up analysis planned. Appropriate action or the need for further investigation can be determined after completion of this analysis. The review of suicidality in pediatric clinical trials with paroxetine and other antidepressant drugs is in DFS under NDA 20-031.

We will continue monitoring citalopram adverse effects in children.

## **Limitations of the Adverse Event Reporting System (AERS)**

The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the U.S reflects underreporting and also duplicate reporting. For any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Therefore, counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing drug risk between drugs.

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Concur:

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