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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE

WITH THE PEDIATRIC SUBCOMMITTEE

OF THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

Monday, February 2, 2004

8:00 a.m.

Holiday Inn Bethesda
Versailles I and II
8120 Wisconsin Avenue
Bethesda, Maryland

1 In conclusion, use of SSRIs and atypical
2 antidepressants is substantial in children and
3 adolescents, and appears to be increasing rapidly
4 every year. Pediatric specialists, pediatricians,
5 and primary care providers continue to be the
6 leading prescribers of these products, and over the
7 past five years, the proportion of pediatricians
8 prescribing these products has nearly doubled.
9 Finally, diagnoses related to the use of
10 these antidepressants are slightly different among
11 the younger pediatric population who are being
12 treated for mood and anxiety disorders, and the
13 adolescent population who are being treated mostly
14 for mood disorders.
15 Thank you.
16 DR. RUDORFER: Thank you very much.
17 This morning we heard from Dr. Murphy
18 about the mandated adverse event review associated
19 with one-year post-exclusivity for some
20 medications. Now, I am pleased to welcome Dr.
21 Solomon Iyasu from the Division of Pediatric Drug
22 Development who will give us a review of that
23 information for paroxetine and citalopram.
24 One-Year Post-Exclusivity Mandated Adverse
25 Event Review for Paroxetine and Citalopram

1 described in the adverse event reports may actually
2 reflect to the underlying disease, because many of
3 these events are also unexpected in other natural
4 progression of the disease or part of the disease
5 picture.
6 It may also be a drug effect or other
7 concomitant medication, or it may actually be lack
8 of effectiveness of the drug, and it is very
9 difficult from these reports to sort out what is
10 going on.
11 Therefore, evaluation of the controlled
12 trials is necessary to sort out causality in terms
13 of the observed adverse events.
14 [Slide.]
15 I am going to continue with the next drug,
16 which is citalopram, but I would like to
17 acknowledge the following individuals for their
18 contribution for their review.
19 [Slide.]
20 Next, I will cover, as mandated by BPCA,
21 citalopram, and will be talking about the adverse
22 events in detail.
23 [Slide.]
24 To give you some background again about
25 citalopram, it's an antidepressant belonging to

1 SSRIs, and marketed by Forest Pharmaceuticals.

2 Its current approved adult indication is

3 for major depressive disorder. The adult dose

4 ranges from 20 to 40 mg/day. There are no approved

5 pediatric indications.

6 The original market approval was July 17,

7 1998, and exclusivity was granted July 9, 2002.

8 [Slide.]

9 Again, to mention some of the relevant

10 safety labeling which already exists, Pregnancy

11 Category C, as I mentioned before, and also a

12 caution against the use in nursing mothers.

13 There is also a Precaution section that

14 mentions, similar to what is observed for Paxil,

15 suicide risk inherent in depression and also the

16 danger of activation of mania and hypomania.

17 Also, additional events mentioned in the

18 precautions, any psychoactive agent may impair

19 intellectual or psychomotor functions, and

20 therefore, care should be exercised in prescribing

21 these medications when individuals have to operate

22 machinery or other things that may require

23 intellectual and motor functions.

24 Seizures is another precaution that is

25 mentioned especially in those with history of

1 seizure.

2 [Slide.]

3 Additional safety information in the

4 Adverse Reaction section is about agitation with

5 the use of citalopram, and also additional

6 premarketing reports which are frequent, impaired

7 concentration, depression, suicide attempt, and

8 confusion; and infrequently reported in premarket

9 reports are aggressive reaction, psychotic

10 reaction, delusion, paranoid reaction, emotional

11 lability, and panic reaction.

12 [Slide.]

13 To give you just a summary of the drug use

14 pattern, it is the fourth most commonly used SSRI

15 in children. Again, use had been increasing in

16 recent years. Pediatric patients account for

17 approximately 3.3 percent of the total U.S.

18 prescriptions of Celexa.

19 Pediatric diagnoses most often linked with

20 its use are depressive disorders,

21 obsessive-compulsive disorder, and attention

22 deficit order.

23 [Slide.]

24 Since marketing, there were over 6,000

25 reports which included also duplicates that were

1 reported to FDA, 79 percent of them were domestic.
2 Less than 5 percent of the reports were in
3 pediatric patients.
4 The top 20 pediatric adverse events were,
5 looking at that, all adverse events related to in
6 utero exposure were unlabeled, which actually
7 happened to be in the top 20 for pediatric adverse
8 events.
9 Adverse event reports for children
10 involving direct exposure were generally similar to
11 those reported for adults.
12 [Slide.]
13 After a manual review of the one-year
14 post-exclusivity period, there were 42 unduplicated
15 reports that were pediatric. Sixteen of them were
16 in utero exposures, and resulted in unlabeled
17 events and one death.
18 There were 26 children involving direct
19 exposure, 8 unlabeled events, and no deaths in this
20 group.
21 Looking at the outcomes, there were 16
22 serious outcomes, 10 hospitalizations, 4
23 life-threatening, and 2 was disability. For the
24 direct exposure group, the dose range was typically
25 5 to 60 mg/day. The median dose was about 20

1 mg/day in these reports.

2 [Slide.]

3 Again looking at the age distribution, in

4 the in utero exposure, most of them female, as well

5 as in the direct exposure group, and age

6 distribution is 0 to 1 in 15 patients, and then

7 most of the direct exposure group, in older

8 children.

9 [Slide.]

10 Looking at the reasons for exposure to

11 citalopram, there were 26 direct pediatric

12 exposures and then 16 in utero exposures. I am

13 going to just focus on the adverse events

14 pertaining to psychiatric, but these are the

15 reasons for why they were exposed.

16 [Slide.]

17 There were only 5 psychiatric events, in 5

18 patients where there were psychiatric events, and

19 these are broken down by labeled and unlabeled

20 events.

21 In the labeled events are the cognitive

22 impairment, aggression, agitation, mania, and

23 delusions, suicidality, and psychotic reaction.

24 Unlabeled events are the violent/homicidal

25 behavior, which were observed in 2 of the patients.

1 [Slide.]

2 Looking at these 5 patients with

3 psychiatric events, there were 4 males and 1

4 female. The age distribution as 6 to 11 years with

5 2; 11 to 16, about 3 of them. Diagnosis in 4 of

6 them was MDD, and 1 case was oppositional defiant

7 disorder, ODD.

8 Concomitant medications were reported in 2

9 patients, Prozac in 1, and another, Keppra and

10 clonazepam. Symptom resolved once citalopram

11 discontinued in 4 according to the reports.

12 [Slide.]

13 In closing, I would like to say there were

14 few psychiatric events that were reported during

15 this one-year post-exclusivity period, unable

16 really to determine causality due to limitations of

17 the AERS database, therefore, we will continue to

18 monitor these adverse events in children.

19 I would like to reiterate the same

20 limitations that I mentioned before with respect to

21 paroxetine when I talked about limitations of the

22 AERS database.

23 Thank you very much for your attention.

24 DR. RUDORFER: Thank you.

25 Dr. Andrew Mosholder will now speak on the

1 Office of Drug Safety Data Resources for the Study
2 of Suicidal Events.
3 Andy.
4 Office of Drug Safety Data Resources for
5 the Study of Suicidal Events
6 DR. MOSHOLDER: Thank you very much.
7 I am very pleased to be here this
8 afternoon. I am going to talk about how we looked
9 at some of our Office of Drug Safety data resources
10 to see if they would be relevant to exploration of
11 this issue.
12 [Slide.]
13 It is very much a team effort and I want
14 to start by acknowledging my colleagues who
15 assisted me.
16 [Slide.]
17 The objective of my brief presentation
18 will be to describe the data resources we have
19 available in the Office of Drug Safety at FDA that
20 are relevant to this issue, and, in particular,
21 looked at two types of databases, the first being
22 the postmarketing surveillance database that Dr.
23 Iyasu just described, and also some
24 population-based epidemiological databases.
25 Also, I will be describing the context of