Mosholder, Andrew D

From: Katz, Russell G
Sent: Tuesday, June 03, 2003 9:24 AM
To: Mosholder, Andrew D
Subject: RE: Paxil and pediatric suicidality

Tab 1

Andy-

Thanks a lot. We'll send over a formal consult ASAP.

Rusty

-----Original Message-----
From: Mosholder, Andrew D
Sent: Tuesday, June 03, 2003 8:56 AM
To: Katz, Russell G
Cc: Willy, Mary E
Subject: RE: Paxil and pediatric suicidality

Hello, Rusty,
Yes, I would be interested in working on this consult. I've confirmed my availability to do so with my team leader, Mary Willy (I'm cc-ing her on this reply).
As I recall, a number of the other SSRI pediatric supplements showed signals for behavioral adverse events. But these were mainly events such as agitation and hypomania, not self-injury (unless, as you suggest, they were similarly obscured by inappropriate terminology).
Regards
Andy

> -----Original Message-----
> **From:** Katz, Russell G
> **Sent:** Monday, June 02, 2003 4:12 PM
> **To:** Mosholder, Andrew D
> **Subject:** Paxil and pediatric suicidality
>
> Andy-
>
> Hi, hope you are well.
>
> We have recently become aware of a presumed association
> between Paxil and suicidality in pediatric patients. We
> received a call from the EMEA a little over a week ago. A
> Dr. Raines told us that the company (GSK) had submitted data
> that demonstrated that use of Paxil in kids was associated
> with increased suicidality compared to placebo, and that the
> company proposed labeling changes; I believe she also said
> that it was in the news, and it was a big issue. Tom and I
> told her that the company had not informed us of any of this,
> and we agreed to look into it.
>
> It turns out that the sponsor was in the process of
> submitting to us a partial response to a question we asked in
> the Approval letter for the pediatric use (you, you may
> recall, were the reviewer). Specifically, we had asked them
> to further elaborate the events subsumed under the preferred
> term "Emotional Lability". We have received this partial
> response, and almost all of these events related to
> suicidality. The bottom line is that when data from the
> controlled trials in depression, OCD, and Social Anxiety are

Plaintiff Exhibit
PX-027

> pooled, for "possible suicide related" events occurring
> during treatment or within 4 days after discontinuation, the
> rate is 0.14/patient-year on drug, and 0.05/patient-year on
> placebo, p=0.02. We have some problems with the methodology
> they used to capture cases, but this is the major finding,
> and it has us worried. The sponsor has not proposed labeling
> changes, and makes a feeble attempt to dismiss the finding.
> We are also awaiting the submission of what the sponsor
> submitted to the UK.
>
> We want to move quickly to evaluate this signal. We are
> planning to look at the NDAs for the other SSRIs to see
> whether or not similar events are being hidden by various
> inappropriate coding maneuvers, but we'd also like to compare
> the drugs in other meaningful ways if we can. We also want
> to call the sponsor very soon and ask some questions about
> their methodology.
>
> We want to send a consult over to you folks, and ask that you
> be assigned the project. Given your history with this
> application and this general issue, we think you would be the
> right person to help us think about the best way to approach
> the data in the other NDAs (and their sponsors), as well as
> to provide ideas for further sources of potentially relevant
> data and possible approaches to better evaluate this signal
> study (e.g., insurance claims databases, etc.). Anyway, I
> wanted to run this by you to see if you have any strong
> objections to being fingered as the guy to do this; if you're
> OK with it, we'll send a formal consult request. Also, we'd
> like you to be in on the phone call, if possible. Of course,
> we recognize that we'd need to get you the submission pronto.
>
> Hope you can do this; if you could let me know soon, either
> way, that'd be great.
>
> Thanks,
> Rusty

Mosholder, Andrew D

Tab 2

From: Laughren, Thomas P
Sent: Tuesday, June 03, 2003 12:53 PM
To: Nighswander, Robbin M
Cc: Katz, Russell G; Racoosin, Judith A; Dubitsky, Gregory M; Mosholder, Andrew D; David, Paul A
Subject: RE: reminder-weekly report

Robbin,

On 6-23-03, Rusty and I first became aware of concerns in the UK about an increased risk of suicidal ideation in pediatric patients taking paroxetine, based on results of new analyses of safety data from a pool of 6 pediatric studies (3 in MDD, 2 in OCD, and 1 in social anxiety disorder). These analyses were actually done in response to requests (included in our 10-10-02 approvable letter the Paxil pediatric supplement) for a more detailed breakdown of events subsumed under the broad heading, "emotional lability;" in particular, we were interested in analyses focusing on events considered to represent suicidality. These results had been sent to the MHRA (UK) before being sent to FDA, due to a difference in the timing of submissions. We have now received these data (in a submission dated 5-22-03, but not received until 5-28-03), as a partial response from GSK to our approvable letter for the Paxil pediatric supplement. These analyses suggest an excess risk of suicidality in patients taking Paxil compared to those taking placebo. The submission to the UK had also included draft labeling to describe this risk, however, I have been informed by David Wheadon, M.D., of GSK, that the MHRA has stated its intent to contraindicate paroxetine in pediatric major depressive disorder, on the basis of these data along with the negative results in the pediatric major depressive disorder studies. GSK does not agree, and they are currently negotiating with the UK and other European regulatory agencies. GSK intends to fully respond to the 10-10-02 approvable letter for the Paxil pediatric supplement by the third week of June, and this will include proposed labeling to address this risk, but also new language regarding the OCD claim in peds. Since the original review of the Paxil supplement, as well as the reviews of most other pediatric supplements for SSRIs, was done by Andrew Mosholder, M.D., and these requests were a direct result of Dr. Mosholder's review, we have submitted a consult to ODS and have asked that this consult be assigned to him in his new position in ODS. We seek his advice on further analysis and interpretation of the Paxil results, as well as more general advice on what might be done to reconsider the pediatric databases for other SSRIs. In addition, we would be interested in his thoughts on further studies that might be done to better understand this signal, e.g., a cohort study using claims based data, perhaps looking at hospitalization for suicidality as an endpoint.

Tom

-----Original Message-----
From: Nighswander, Robbin M
Sent: Tuesday, June 03, 2003 11:52 AM
To: Katz, Russell G; Laughren, Thomas P
Subject: FW: reminder-weekly report

Rusty and Tom:

Although I included a brief description in last weeks report, as you can see, John would like a longer summary. Last weeks report is attached.

Thanks

Robbin

<< File: OND1 Weekly Report May 28 2003.doc >>

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Tab 3

REQUEST FOR CONSULTATION

TO (Division/Office):			FROM:	
Mail: ODS (Room 15B-08, PKLN Bldg.)			**HFD-120/Division of Neuropharmacological Drug Products**	
DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
6-5-03		**20-031/SE5-037**	**Minor Amendment**	**5-22-03**
NAME OF DRUG	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Paxil (paroxetine HCl) Tablets			**Selective Serotonin Reuptake Inhibitor (SSRI)**	

NAME OF FIRM: **GSK**

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

COMMENTS/SPECIAL INSTRUCTIONS:

We have received a partial response (5-22-03) from GSK to our approvable letter for the Paxil pediatric supplement, including results of new analyses of safety data from a pool of 6 pediatric studies (3 in MDD, 2 in OCD, and 1 in social anxiety disorder). These analyses were in response to requests in our 10-10-02 approvable letter for a more detailed breakdown of events subsumed under the broad heading, "emotional lability;" in particular, we were interested in analyses focusing on events considered to represent suicidality. These analyses have been done, and they suggest an excess risk of suicidality in patients taking Paxil compared to those taking placebo. Since the original review of the Paxil supplement, as well as the reviews of most other pediatric supplements for SSRIs, was done by Andrew Mosholder, M.D., and these requests were a direct result of Dr. Mosholder's review, we ask that this consult be assigned to him. We seek his advice on further analysis and interpretation of the Paxil results, as well as more general advice on what might be done to re-evaluate the risk of suicidality in the pediatric databases for other SSRIs. In addition, we would be interested in his thoughts on epidemiological studies that might be done to better understand this signal, e.g., a cohort study using insurance claims based data, perhaps looking at hospitalization for suicidality as an endpoint.

If you have any questions, please feel free to contact the Safety Group Team Leader, Dr. Judith Racoosin (x4-5505), or the Project Manager, Mr. Paul David (x4-5530).

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
6/6/03 12:39:48 PM

Mosholder, Andrew D

From: Mosholder, Andrew D
Sent: Thursday, June 19, 2003 4:30 PM
To: Katz, Russell G; Laughren, Thomas P; Andreason, Paul J; Stasko, Robert; Racoosin, Judith A; David, Paul A
Subject: Paroxetine suicidality data in 4-11-02 submission

Tab 4

Hello all,

During today's meeting there were some questions about exactly what data the sponsor provided on this topic, and why we asked for what we requested in the approvable letter. This prompted me to look back at the approvable letter, the original ISS for the supplement (which is still available via the EDR) and my clinical review from last October.

The sponsor did provide a line listing of all patients with serious adverse events (ISS Table 7.8) for both drug and placebo. This table showed suicide attempts such as overdoses coded as "emotional lability," which is how we knew that was being done. Using Table 7.8, I noted in my review that there was a higher rate of suicidality-related serious adverse events for paroxetine than for placebo in the acute trials, but that this was not statistically significant.

Additionally, the sponsor provided a line listing for all adverse events coded as "emotional lability," "hostility," or "agitation" (ISS Table 6.14). Although it included nonserious events as well as serious, it did not include placebo patients, only paroxetine patients. This table also showed suicide attempts coded as emotional lability.

As a result of this situation, we asked for the following in the approvable letter:

> Table 6.14 in the ISS listed paroxetine treated patients who experienced adverse events coded under the terms hostility, emotional lability or agitation. However, the table did not include placebo patients, nor did it include psychiatric adverse events that were coded under other terms. Please prepare an expanded version of this table, including all psychiatric and behavioral adverse events, and also those that occurred among placebo patients...

We also asked GSK to provide a rationale for their coding of suicide attempts as emotional lability.

Also, the data from the Social Anxiety Disorder trial was still blinded when the supplement was submitted.

I hope this historical information is helpful.

-Andy

Mosholder, Andrew D

Tab 5

From: Mosholder, Andrew D
Sent: Monday, June 23, 2003 10:24 AM
To: Racoosin, Judith A
Subject: RE: coding dictionary for paxil peds MDD supplemental NDA

Hi Judy,

Here's what is says in the Paxil pediatric supplement ISS, section 6.3.1.

> AEs were coded from the verbatim terms provided by the investigators by using the World Health Organization Adverse Reaction Terminology (WHO ART) codelist. These terms were then mapped to Adverse Drug Experiences Coding System (ADECS) classification to provide body system and preferred term. The ADECS is a COSTART based dictionary. Gender specific events were tabulated separately from gender non-specific events to allow percentages to be corrected for gender. As stated previously, the coding process differed between the acute clinical studies and acute clinical pharmacology Study 715 (i.e., for Study 715, terms were not mapped to ADECS). Therefore, body system and preferred terms will differ between these studies.

Of course, study 715 is not relevant here.

-Andy

> -----Original Message-----
> **From:** Racoosin, Judith A
> **Sent:** Monday, June 23, 2003 10:14 AM
> **To:** Mosholder, Andrew D
> **Subject:** coding dictionary for paxil peds MDD supplemental NDA
>
> Hi Andy,
> Do you know which coding dictionary was used for the paxil
> peds MDD supplemental NDA? You have probably already told me,
> but I just can't recall.
>
> thanks
> Judy

Mosholder, Andrew D

From: Pamer, Carol
Sent: Tuesday, June 24, 2003 9:13 AM
To: Racoosin, Judith A
Cc: Mosholder, Andrew D; Singer, Sarah J
Subject: FW: Suicide-related terms in WHO-ART?

Tab 6


Clear Day Bkgrd.JPG

From our coding guru, Sally Singer.

Carol

-----Original Message-----
From: Singer, Sarah J
Sent: Tuesday, June 24,2003 9:10 AM
To: Pamer, Carol; Goetsch, Roger A; Piazza Hepp, Toni D
Cc: Lu, Susan
Subject: RE: Suicide-related terms in WHO-ART?

Hi Carol,
I have an old COSTART manual; SUICIDE ATTEMPT did exist. The manual has a COSTART to WHOART translation table which states that SUICIDE ATTEMPT also existed in WHOART.
-Sally

-----Original Message-----
From: Pamer, Carol
Sent: Tuesday, June 24, 2003 9:07 AM
To: Goetsch, Roger A; Piazza Hepp, Toni D; Singer, Sarah J
Cc: Lu, Susan
Subject: Suicide-related terms in WHO-ART?

Good morning--

A question has come up about the way that suicides/suicide attempts were coded in a recent NDA supplement. Apparently the company chose a term like "emotional lability" when in actuality most were suicide attempts. They used WHOART and COSTART as their dictionaries (see below), and a dictionary I am not familiar with, ADECS. We are talking about CSK and Paxil pediatric supplement. FYI. How can we verify that WHOART has a specific term for suicide/attempts? I don't have a copy of a WHOART reference, if there is one around here. It would also be helpful to have someone verify for me that COSTART has Suicide Attempt and perhaps others for the same. Too many brain cells have come and gone for me since the era of COSTART!!

Thanks!

Carol

Rappaport, Bob A; Shames, Daniel A; Simon, Lee; Smith, Nancy D (CDER); Soreth, Janice M; Talarico, Lilia; Throckmorton, Douglas C; Trontell, Anne E; West, Robert L
Subject: Regulatory Briefing - Paxil SPECIAL
When: Tuesday, September 16, 2003 2:00 PM-4:00 PM (GMT-05:00) Eastern Time (US & Canada).
Where: CDER OCD LAPTOP; CDER EOS PROXIMA; CDER WOC2 6FL-G Conf Room

NDA 20-031/S-073
Paxil (paroxetineHCl) Tablets
This supplement provides for controlled clinical studies in children and adolescents with major depressive disorder (MDD) and obsessive compulsive disorder (OCD). The controlled studies in the pediatric population with MDD demonstrated that pediatric patients who received Paxil had a higher incidence of suicidal ideation/attempts. This supplement received an approvable action on October 10, 2002. GlaxoSmithKline has not submitted a complete response to this action letter.

Andy

Tab 9

> -----Original Message-----
> **From:** David, Paul A
> **Sent:** Wednesday, August 27, 2003 10:00 AM
> **To:** Mosholder, Andrew D
> **Subject:** RE: JAMA article on Zoloft in pediatric depression
>
> Thanks for the reprints Andy. It made for some interesting
> reading. I forwarded them to the peds suicide team as well
> as the psych reviewers.
>
> I've been working with Jennifer Mercier on the Regulatory
> Briefing, and she is going to get back to me in a few days
> with the date. I believe that you are Tarek will be presenting.
>
> We're also starting to get responses from our pediatric
> suicide data request letters, and I believe that Judy is
> going to talk to you about looking at the data. I'm
> receiving lots of desk copies so it should not be a problem
> to forward the submissions to you.
>
> -Paul
>
> -----Original Message-----
> **From:** Mosholder, Andrew D
> **Sent:** Wednesday, August 27, 2003 9:30 AM
> **To:** David, Paul A
> **Subject:** JAMA article on Zoloft in pediatric depression
>
> Hi Paul,
> I downloaded the JAMA articles referred to in today's Daily
> Clips. Please share with anyone else over their who's interested.
> As you recall, we turned down this supplement because each
> trial by itself failed. This article combines the two trials
> to show a statistically significant effect. I don't see
> where they've said that the individual trials failed and they
> had to pool them to have a result. Instead, the authors tout
> the combined analysis for having a large sample size...talk
> about spin!
> Andy
>
> << File: Varley editorial JAMA.pdf >> << File: Wagner et al
> JAMA.pdf >>