

**U.S. Food and Drug Administration**

**Media Teleconference:  
FDA Announces Label Change for All Sleep Disorder Drug Products**

**Moderator: Kimberly Rawlings  
March 14, 2007  
11:00 am CT**

**TRANSCRIPT**

Coordinator: Welcome and thank you for standing by.

At this time, all participants are in a listen-only mode.

During the question and answer session, please press star-1 to ask a question.

Today's conference is being recorded. If you have any objections, you may disconnect at this time.

Now, I will turn the call over to Ms. Kimberly Rawlings.

Ma'am, you may begin.

Kimberly Rawlings: Thank you.

As she said, this is Kimberly Rawlings with the Office of Public Affairs. And I thank you all for joining us today to participate in FDA's media call regarding our recent announcement on a label change for all sleep disorder drug products.

Today, to provide brief remarks and to entertain your questions, we have Dr. Russell Katz, who is the director of the Division of Neurology Products in the

Office of Drug Evaluation I at the Center of Drug Evaluation and Research here at FDA.

We ask that you please listen intently. He will provide detailed remarks and then following his remarks, we will send the call over to Q&A.

Thank you.

Dr. Katz?

Russell Katz: Hi, and thanks, Kimberly.

As you know, the agencies announced today that we had asked sponsors of sleeping drugs to change their labeling to describe two events that we believe are serious and about which practitioners and patients need to know.

One is severe anaphylaxis or angioedema. These are potentially severe allergic reactions that can affect patient's ability to breath and can affect other body systems as well and can even be fatal at times.

These events are relatively rare as far as we can tell. We - the changes are based on - the changes that we have proposed that sponsors adopt in their label are based on reports that we have received from the use of the drug in a post-marketing arena.

They are rare but because these are drugs that are intended to (aug) their patient's state of consciousness, that is to say these are drugs that are intended to people to sleep, it might be difficult for a patient to know they're having this event if they're falling asleep or report to someone that they are having this event as they are falling asleep.

So we thought it was very important for practitioners to let patients know that this kind of event can occur with the use of the drug even though it is rare. And that might factor into the decision as to whether or not to take these drugs or to continue taking them.

This allergic reaction can occur on the first use of the drug or they can occur later on.

The other potentially serious adverse event that we are asking sponsors to include in their labels is something we call sleep driving and other complex behaviors. And these are - as the name imply, complex behavior is going to occur in the middle of the night when the patient might wake up after having taken one of these medications to go to sleep.

It's not entirely clear if they are awake or asleep in this state, but nonetheless, they can engage in complex behaviors like driving and/or other behaviors.

And of course, that could be - as you might imagine, potentially dangerous to both the patient and to others as well. So in addition to asking sponsors of these drug products to include these events in their label, we have asked them to issue Dear Healthcare Practitioner letters so that physicians and prescribers can be aware of this.

And in addition, we have also asked sponsors to produce what we called medication guides. These are leaflets in effect that described the important adverse events that the patients might experience when they one of these drugs.

We are specifically asking for medication guides so that patients can be aware of the sleep driving and complex behavior issue because we do believe that there maybe things that patients can do to reduce the risk of the occurrence of these middle of the night complex behaviors, including making sure that they take the right dose because these events can occur - more likely to occur with higher than appropriate doses.

And also, they can occur in association with other drugs that can affect the nervous system and especially alcohol. So we do believe that patient should be aware that there are behaviors that they can engage and that could decrease the risk of these events occurring; namely, to refrain from alcohol or other drugs that depress the nervous system and to make sure they take the right dose.

So we believe it's important for patients to know that. So in addition to the publicity (appending) to the press release today and the Dear Doctor letters that we expect sponsors to send, we do believe the medication guides are the appropriate way to directly inform patients about these potential series events.

So, there have not necessarily been reports of all of these events with all the drugs in this class, but we believe that that's really probably related to factors other than the capability for the drug to do it, whether it's because some drugs are relatively new and there haven't been many reports of any sort or whether they're very, very old and we wouldn't expect it to see reports of these behaviors.

So - but nonetheless, we do believe that all of the drugs in the class are capable of producing these adverse events. And so we've asked all the drugs to adopt the language and to issue the letters to the healthcare practitioners and to produce these medication guides.

So I guess I'll stop there and to see if there are any questions.

Kimberly Rawlings: Thank you, Dr. Katz.

At this time, (Tracy), we'd like to open the line for questions from  
credentialed press only. Again, this call is for credentialed media only.

Thank you.

Coordinator: Thank you.

We will now begin the question and answer session.

If you would like to ask a question, please press star-1. You will be prompted  
to record your name. To withdraw your question, you may press star-2.

Once again, if you would like to ask a question, please press star-1.

One moment, please.

Ms. (Julie Gorman) is our first - (going to) ask the question first.

(Julie Gorman): Yes. Thank you, Dr. Katz.

Have any company...

((Crosstalk))

Kimberly Rawlings: Tell us your organization, please.

(Julie Gorman): Oh sure. This is (Julie Gorman) with Reuters News agency.

Kimberly Rawlings: Thank you.

(Julie Gorman): Have any companies told the FDA yet that they will conduct some additional trials about the risk per FDA's request?

Russell Katz: No, not yet.

Woman: Do you have a follow-on, (Julie)?

(Julie Gorman): Do you expect to get any request for these kinds of...?

Russell Katz: Well, of course, it's easier for sponsors to adopt labeling than to conduct trials, but we hope to be in discussions with sponsors to try to get them to do this.

(Julie Gorman): Okay.

Russell Katz: So we'll be working with them but whether or not we will get any of these trials, I just don't know.

(Julie Gorman): Okay. Thank you.

Kimberly Rawlings: Thank you.

Next question, please.

Coordinator: Ms. Jennifer Corbett, you may ask your question.

Jennifer Corbett: Yeah. Hi, Jennifer Corbett with Dow Jones.

I'm wondering if all of the manufacturers have agreed in labeling (changes).

Russell Katz: Pretty much all have agreed to the changes that the language that they adopt maybe slightly different one to the other depending upon whether they've had a case reported of one of these events or another or whether they have.

And so, we are in discussions with at least one sponsor. But for all intents and purposes, all have agreed.

Jennifer Corbett: Can you say who the one who (don't hold at it)?

Russell Katz: I can't, no.

Jennifer Corbett: Okay. (Unintelligible).

Russell Katz: Yeah.

((Crosstalk))

Russell Katz: You have to try.

Kimberly Rawlings: The next question, please.

Coordinator: Ms. (Donna Young), you may ask your question.

(Donna Young): Hi, yes. I have a couple of questions.

Are the letters that you talked about in the press release, the December 2006 letters, are they available on the Web site? And it says in the press release that you've been working with consumers on these risks when before this have you notified consumers about the risk and how soon will you have a draft of the medication guides or the actual medication guides available?

Russell Katz: Yeah. Let me - the first part of your question was...

(Donna Young): The December 2006 letters, will they be available?

Russell Katz: (They're) on the Web. I...

Kimberly Rawlings: Some of the labeling is...

((Crosstalk))

Russell Katz: ...the other question is the letter, the December 2006 letter and whether they are posted on the Web, I don't think they are...

Kimberly Rawlings: No, that is not posted on the Web.

((Crosstalk))

Kimberly Rawlings: It has to be (unintelligible) before it can be posted.

(Donna Young): And the labeling, did - Kim, did you say that some of the labeling is available on the Web site?

Kimberly Rawlings: It should be, if not now, it should be very soon.

(Donna Young): Okay. And then the medication guides, (how)...

((Crosstalk))

Kimberly Rawlings: Yeah.

(Donna Young): ...will those be available and how - have you given them a deadline for distributing them to pharmacies?

Russell Katz: Not a deadline for distributing to pharmacies. We have also - we are working internally to produce a portion of the med guide, which would be standard language that all would adopt.

And then the rest of the med guide would be more specific to each individual drug outlining what the specific adverse events that you might see with that drug.

I think we - in the letter asked for them to submit their med guide by the beginning of May, but we don't have a deadline for when they will actually be handed out to patients and be available in pharmacy.

The other part of your question, I think, you asked that we set in the press release that we have been working with patients, I don't believe it says that we have been working with consumers.

Woman: (Or the company).

Russell Katz: I think we've been working with the companies to produce the medication guides, which will be given to consumers.

So, the other part of labeling, which I didn't describe as being changed in my opening remarks, but (I'm suggesting now for completeness) is that we've asked - there's a section in the labeling for the physician to read. It's called Information for Patients.

This is information that we believe that the physician should tell the patients. And so we've ask for these events to be included in that section of labeling so that the physicians will tell patients that this thing could possibly occur.

And this provides some, we believe, a necessary redundancy in the system so that we're making every reasonable attempt to get the message to the patients. We are telling physicians to tell patients, and we are having sponsor produce some med guides, which will be actually be given to patients so they can read it for themselves.

(Donna Young): Exactly.

So when will you have a draft of the med guides available on your Web site like you did with the (ADAC) drugs to put the, you know, like a draft of those med guides? Will FDA...

((Crosstalk))

Russell Katz: (That I can't) (unintelligible). I say I don't know, first of all, whether or not there will be draft to the med guides. I just don't know the answer to that question up on the Web.

But as I say, we have an early May deadline for the sponsors to submit their specific individual med guides to us.

(Donna Young): Uh-huh.

Russell Katz: Then of course, we have to review those.

(Donna Young): Exactly.

Russell Katz: And we will presumably negotiate with sponsors about exactly what those med guides ought to say and then hopefully after that they will be available.

(Donna Young): And it sounds like you have a number of adverse drug events reported or what actually triggered this...?

((Crosstalk))

Russell Katz: Well we do have numbers. I'm not aware that we can release those numbers. I just don't know whether we can do that or not.

Again, we became aware of the angioedema reports in the wake of the marketing for one of the more recent - I guess the most recently approved hypnotic.

And then when we - (so those) after a brief period of marketing, we went back and look at the whole class of hypnotics, which are - (it's) a technical term for the drugs that are taken to - put people to sleep.

(Donna Young): Which one was the most recently approved - oh I'm sorry, which one was the - what - you said the most recently approved one?

Russell Katz: Ramelteon.

(Donna Young): Okay.

Russell Katz: And we sort of went with that, and then we went back and look at the entire class and they all have cases reported with all of the drugs, certainly not just that drug.

And the sleep driving, then the complex behaviors became - we became aware of about a year ago based on the reports that were made public. And we went back and look at all of the drugs in that class as well.

And those are, of course, complicated to interpret as to whether or not a particularly case actually is one of these sleep driving cases or whether it's something else. So - but again, we've looked now at the entire class and believe that the entire class is capable of producing those events as well.

(Donna Young): Thank you very much.

Russell Katz: Uh-huh.

Kimberly Rawlings: Our next question, please.

Coordinator: Ms. Catherine Larkin, you may ask your question.

Catherine Larkin: Hi. Catherine Larkin with (Bloomberg News).

Kimberly Rawlings: (Hi). Can you please give your organization as well?

Catherine Larkin: Sure. It's Catherine Larkin with Bloomberg News.

I just have a quick follow-up question for Dr. Katz.

You said you can't release the numbers of the adverse event reports that you've received, but can you give us a general percentage as to how many patients may have these risks or if there's any way we can give anymore information to our readers?

Russell Katz: Yeah, you know, it - yeah, first of all, I mean as far as the numbers, I just don't know whether or not the rules permit me to give you the numbers.

But we do think there are more cases - let me just say, there are more cases reported of the allergic reactions than there are of the complex behaviors in sleep driving events.

It's - we think by - as far as we can tell, by any definition you might want to use, they're rare. Of course, the problem with post-marketing reports is you let - you're pretty confident that you're never learning about all of the ones that occur because as you know, the post-marketing reporting system that we have is primarily a voluntary system.

No one is required to report an event to the agency even if they think it might be related to drug and there are many vagaries in the system. And so, it's - we know that we - whatever numbers we do get even for serious events, which we think both these are, are considerable under report.

So it's very difficult to know exactly how many of these are recurring. As far as the reports that we have received of these events, they're rare. But I - it's hard to say much more than that.

Catherine Larkin: Thank you.

Kimberly Rawlings: Our next question, please.

Coordinator: Our next question comes from Lauren Neergard of the Associated Press.

Lauren Neergard: Hi, Dr. Katz.

(Unintelligible)...

((Crosstalk))

Lauren Neergard: ...talking back to these incidents, question again, you said that you became of that about aware about a year ago based on some public reports. Was that the (Patrick Kennedy) incident that sparked this?

Russell Katz: No, no, no. There were other reports presented at the professional meetings.

Lauren Neergard: Okay. And had there been any previous FDA warnings?

Russell Katz: About...

Lauren Neergard: About the drugs?

Russell Katz: ...these specific events?

Lauren Neergard: Yeah, the behavior - the sleep behaviors...

((Crosstalk))

Russell Katz: No, there were - there was language and also essentially class language in all of these drugs about behavioral changes that can occur, that sort of things.

Lauren Neergard: Uh-huh.

Russell Katz: That's been in the label for quite a while, all the labels, I believe, for quite a while. But the specific behaviors -- sleep driving, sleep eating, that sort of thing, no, I don't believe there was language about that.

Sleep walking, there might have been, but again we do believe that sleep walking, whatever, that is exactly is different from these behaviors. The sleep walking I - is considered - this may not be technically correct, but it's considered sort of more of a reflex, patients get up and they just walk and they can hurt themselves. These behaviors are very complex behaviors. They are different.

Lauren Neergard: How are they different?

Russell Katz: Well they're different fundamentally because of the complexity, because - people get up. They get their car keys and they go drive, which is very different from just getting up and taking two steps and maybe walking into a wall or falling down the stairs which is more what sleep walking is.

So, this - and there are other, again, behaviors, again, sleep eating, making phone calls, the labeling need to describe having sex while essentially asleep, so there are many complex behaviors that people can engage in under the influence of these drugs.

Lauren Neergard: And to go back to the incidents, would it be fair to say that you have dozens of reports, a dozen reports, (unintelligible)?

((Crosstalk))

Russell Katz: It's not much more than that.

Lauren Neergard: Which one?

Russell Katz: Dozens or dozen...

((Crosstalk))

Lauren Neergard: A dozen?

Russell Katz: Yeah. But again, I can't - I would tell you, I'm just not aware if that's - that the numbers are releasable, but we can - (I suppose) find out (unintelligible).

Kimberly Rawlings: Yeah, I'll find out.

((Crosstalk))

Lauren Neergard: Yeah. I think if they are regular post-marketing reports, I think, that's releasable, I mean you all have an ARIS database that's public.

Russell Katz: No, I know, but it's a question of how it becomes - I don't know. I - we'll find out.

Lauren Neergard: Okay. But in the meantime, I can characterize it as about a dozen?

Russell Katz: No. It's more.

((Crosstalk))

Russell Katz: but again, which reaction you're talking about, are you talking about angioedema or...

((Crosstalk))

Lauren Neergard: No, the complex sleep behaviors.

((Crosstalk))

Russell Katz: ...(they're complex) - yeah, it's more than that.

Lauren Neergard: Okay.

All right, if you all could figure out exactly what kind of number range you can give me and get back to me, that would be great.

Thanks.

Russell Katz: Uh-huh.

Kimberly Rawlings: Our next question.

Coordinator: (Tracy Parks) of NBC. You may ask your question.

(Tracy Parks): Thank you.

I'm wondering in addition to (what) - you're working with now with the manufacturers as the next step, is there any talk about further evaluating the safety and availability of these drugs?

And second, given the fact that they're having some high-profile type sleep driving type cases that people are aware of, what can you say to the public today that we can share with them to reassure them that these drugs are safe to use for the most part?

((Crosstalk))

Russell Katz: Again, I don't think we are reconsidering whether or not the drugs ought to be available. I think - we think as I said that these are both useful for an important medical problem that many people have, and that these particular events are rare, whatever exactly the numbers are. And again, we can get back to that.

But - so, we think these are rare and we do think that what's important is that people be aware that this can occur and in particular, with regard to the complex sleep behaviors, we do believe that the risk is increased by certain things that the patients can do, which isn't to say that if they don't do those, the risk is zero.

But we do believe that increasing the dose beyond what was recommended, taking alcohol in association with these drugs, and taking other nervous system active drugs or depressant drugs can increase the risk.

So we really want people to know that these things can occur, and in particular we think that the sleep behaviors can be to, perhaps, large extent mitigated by behaviors that the patients can control.

So they need to know that when they considered taking it or continuing to take these drugs, and they need to know what they can do to prevent at least one of these events or at least markedly reduce the risk.

We don't think that, as I say, that these are sufficiently frequent that it would cause us to reevaluate whether or not the drug should be on the market (here). We don't believe that it reaches that level.

But we do believe the labeling needs to be changed to make this prominent so that physicians know it. We do believe that it's important to make the information public so both physicians and patients will be aware of it and to have this medication guide.

And I - you know, our view at the moment anyway is given the frequency of these events that that should - that's an appropriate response to this information.

(Tracy Parks): So the - you said that the behaviors can be mitigated by things the patient can control, for example, you mentioned taking the proper dosage, not mixing it with alcohol. So then the events of - the types of behaviors that you saw looking specifically at the complex sleep behaviors in all of those cases where the cases for people overdosed or mixed with alcohol or other drugs?

Russell Katz: No. As I say, it's not to say that if you don't (think) (unintelligible) behaviors, your risk reduce to zero. But there were many cases in which these were complicating factors or concomitant factors.

Kimberly Rawlings: Our next question, please.

Coordinator: Stephanie Saul from the New York Times. You may ask your question.

Stephanie Saul: Hi. It's Stephanie Saul from the New York Times. I have a couple of questions.

How unusual are the medication guides? (How frequently)...

((Crosstalk))

Russell Katz: You know, that's - I don't know how common medication guides are. I don't - they're not, you know, extraordinarily common. I think - we think when there is a serious adverse event that is potentially preventable, that's the time that we ask sponsors to produce them.

But I'm not in a position to know how many there have been, let's say, in the past year or since the system was produced. So I - there maybe another way you could get that information, but I certainly don't have that information.

Stephanie Saul: Okay. Are - in the adverse event reports that you look at, where there any deaths attributable to this unusual sleep related behavior?

Russell Katz: No, no.

Stephanie Saul: We've had several consumers call and say that their mother died after, well, sleepwalking outside, after taking the medication or there were people killed in automobile accidents after taking Ambien that they believed were the result of sleep driving. You're not aware of any of those?

Russell Katz: No.

Stephanie Saul: Okay.

Now, my understanding is that the use of the term “rare” is kind of a term of art in the FDA. That it means something like 1 in 10,000 or one in - I believe this term is 1 in 10,000.

Are you using in that context? I mean how do you define rare?

Russell Katz: Again, it's - you're right. People have different definitions.

I'm just (low) - I would say, again, you have to understand that we deal with reporting rates as opposed to true incidents.

Stephanie Saul: Uh-huh.

Russell Katz: In other words, the true incident is how many cases there are divided by the number of people who took the drug or the number of people who took the drug over a certain period of time.

Stephanie Saul: Uh-huh.

Russell Katz: We don't have that information directly. We - all we have are reports to us, and we have to make some assumptions about how many people have actually been exposed to these drugs based on prescription sales and that sort of things.

So we don't really know what the actual true incidence is or we know our reporting rates and as I say, we know that those - that these events are underreported. We just don't know by how much.

Stephanie Saul: Okay.

Russell Katz: Some people would say as many as - we only hear about 5% or 2% or 10% of cases, and really there are many more cases out there.

So, it's hard - again, without (dealing) specific numbers and whether or not those are releasable in this phone call, it's hard to know. But the reporting rates - again, reporting rates are fairly low. I mean they're rare by any reasonable definition. (Again, we just don't know).

Stephanie Saul: I actually have the ARIS database on a CD-Rom, the ARIS database for Ambien.

The problem that I've had getting the numbers out is that in some cases, the people were taking more than one medication. So it's really hard, for me as a layman, to decide whether to attribute those...

((Crosstalk))

Russell Katz: Well I think it's hard for everybody to do that. And one of the problems with - we're trying to interpret data that submitted to the ARIS database.

Stephanie Saul: Uh-huh.

Russell Katz: There maybe in any given case of an event. There maybe many other factors described that could positively account for it, instead of the one you're interested in or there could be no information provided, which makes it equally difficult.

So we have to do our best to try and identify cases that we think could be related to the drug. There's no obvious other confounding effect...

((Crosstalk))

Stephanie Saul: And I would also be interested in getting that data if it's released or the results of your review, and I have...

((Crosstalk))

Woman: ...for that.

Stephanie Saul: And I have one more question.

Russell Katz: Okay, yes.

Stephanie Saul: What are the other adverse events that you - the other unusual behaviors that you identified other than sleep eating and sleep driving?

Russell Katz: Well we described - the described events in the label the language that we've asked sponsors to adopt -- phone calling, having sex, the driving vehicle, eating, cooking, that sort of thing.

Stephanie Saul: Okay.

Kimberly Rawlings: And we'll have to take one last question from...

Stephanie Saul: Thank you.

Kimberly Rawlings: ...another caller.

Coordinator: Ms. (Roni Raymond) from New York Times. You may ask your question.

(Roni Raymond): Yeah. I just want to make a couple of things. But I just want to make sure when you said no deaths, there were no deaths from the anaphylactic shock or - and the other - and that other effects you mentioned as (unintelligible)...

((Crosstalk))

(Roni Raymond): ...complex behaviors?

Russell Katz: That have been reported to us, that's correct, right.

(Roni Raymond): Okay.

One thing is, is there any way for, (you know), a consumer to evaluate and compare different sleep (aids) in terms of their possibility of creating these effects and is there - are there any - have you identified any individual risk factors that would place a person at higher risk for these?

Russell Katz: No. Again, given the data that we've seen and, again, given usage, that is to say some drugs that used much more than other drugs. And so you naturally get more reports with those.

So it's very difficult to say one drug does it more frequently than another drug. And we don't think the data allow us to make those distinctions. So, I don't think there is much that we or the consumer could look to try differentiate the drugs on that basis.

(Roni Raymond): And individual?

Russell Katz: (Unintelligible) another part to your question.

(Roni Raymond): Any individual risk factors that someone - if someone had allergic reaction (unintelligible) other drugs or...

((Crosstalk))

Russell Katz: So again, we - as we've mentioned, we do think, at least, for the behavioral changes, the complex behaviors, we think that taking a dose higher than is recommended, taking alcohol, taking other drugs that might have similar effects, those all seems to increase their risk.

(Roni Raymond): Uh-huh.

Russell Katz: So we absolutely think people should be aware of that.

(Roni Raymond): And also, is there - isn't there a recommendation that these drugs not be taken more than - for than a few weeks?

Russell Katz: No. What - different drugs have done controlled clinical trials with different duration and those durations that described in labeling. There's also language in labeling that it says that the insomnia persists beyond a week or ten days, that a physician should think that maybe there are some underlying cause for it other than just simple insomnia.

But none of the labels say that they should only - any of these drugs should only be used for a particular duration.

Kimberly Rawlings: Thank you, Dr. Katz.

At this time, we'll have to conclude our tele-briefing. I apologize if you all didn't have an opportunity to ask your question.

If you do have any outstanding questions, I ask that you refer them to the Office of Public Affairs, to myself, Kimberly Rawlings or Sandy Walsh.

My email address is kimberly.rawlings, spelled R-A-W-L-I-N-G-S, @fda.hhs.gov, and Sandy Walsh can be reached at S-A-N-D-R-A.

Sandy Walsh: No, it's sandy, S-A-N-D-Y, .walsh, W-A-L-S-H, @fda.hhs.gov.

Kimberly Rawlings: Thank you very much.

Coordinator: Thank you for participating in today's conference call. You may disconnect at this time.

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