UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

PEDIATRIC ADVISORY COMMITTEE MEETING

Washington, D.C.

Tuesday, September 23, 2014

DR. ROSENTHAL: Jeff Rosenthal. I agree.

DR. HUDAK: Mark Hudak. I concur.

DR. LARUSSA: Phil LaRussa. I concur.

DR. CUNNINGHAM: Melody Cunningham. I agree.

CHAIRMAN TOWBIN: Thank you. We will return at 130 to talk about Singulair or montelukast, and I can't thank you enough for your help this morning.

DR. ELLENBERG: For those in the committee, if you would please remember that you should not be talking about any topics that are before the committee during your lunch break. Thank you very much.

(LUNCH BREAK)

CHAIRMAN TOWBIN: I think that were ready to begin the afternoon session or shall I say the postprandial session. We're going to talk about montelukast or Singulair. Dr. Radden, I think, is going to help us.

Dr. Radden is a family practice

physician who received her medical degree from the Uniformed Services University of the Health Services and completed internship and residency at the Malcolm Grow Medical Center on Andrews Air Force Base with the National Capital Consortium. She recently separated from the United States Air Force after 14 years of service -- thank you -- and joined the United States Public Health Service. Prior to joining the FDA, she practiced at Dover Air Force Base where she served as the medical director of the family practice clinic in addition to the deputy chief of the medical staff. Dr. Radden.

DR. RADDEN: Good afternoon. As stated, I'm going to discuss Singulair, or montelukast sodium. I will be following this outline and giving a brief history of neuropsychiatric events associated with montelukast use.

Singulair is a leukotriene receptor antagonist indicated for the prophylaxis in chronic treatment of asthma, acute prevention of exercise-induced bronchial constriction or EIB,

and relief of both perennial and seasonal allergic rhinitis symptoms. Singulair is approved in adults and pediatric groups down to 6 months based on the indication, but I direct your attention to the approval for EIB, which will be the focus of this review.

Singulair is available in multiple dosage strengths and formulations including chewable tablets and granules. Once daily dosing is recommended for all indications except the EIB indication, which recommends patients take one tablet at least two hours prior to exercise not to exceed more than one dose in a 24-hour period. You can see the specific dose recommendation for each group on the slide.

Singulair was originally approved in February 1998. The pediatric label change prompting this review occurred in March 2012 and expanded the EIB indication to include patients 6 to 14 years of age. PREA studies were waived in patients less than five years of age.

The evidence supporting the use of

Singulair in patients ages 6 to 14 years for EIB are drawn from the results of a multinational, randomized, double-blind, placebo-controlled, crossover study using the 5 milligram chewable tablet in this age group. The results were further supported by extrapolation of data from the trials conducted in patients 15 years and older to support the initial EIB indication.

Singulair was given as a single dose and then exercise challenge testing was performed at 2 hours and 24 hours post-dose. Results for the primary endpoint, maximum percent fall in FEB one after exercise challenge testing at 2 hours post-dose demonstrated a statistically significant reduction in EIB compared to placebo. Although a statistically significant reduction was also seen at 24 hours post dose, when the individual responder data was examined not all patients were uniformly protected at the 24-hour time point.

Note that labeling states that daily administration of Singulair for the chronic treatment of asthma has not been established to

prevent acute episodes of EIB. Use statements were updated in section 8.4, and pediatric information relating to this expanded indication in patients 6 to 14 years of age was included throughout labeling.

Now will discuss relevant safety labeling. Singulair is contraindicated in patients with a known history of hypersensitivity to any component of the product. Note that Singulair contains lactose. As you can see, there are six subsections to the warnings and precautions section, and I would like to discuss the neuropsychiatric event subsection a little further as these events will appear again later.

Section 5.4 discusses postmarketing reports that include a range of neuropsychiatric events related to aggression and agitation, anxiety and depression including suicidality, sleep and cognition, and motor disturbances. The section goes on to note that the clinical details of some of these reports appear consistent with a drug-induced effect and advises patients and

prescribers and on management with regards to the potential for these events. The most common adverse reactions in controlled trials are noted here and appear to be related to infectious etiologies. The adverse reactions noted in the clinical trials for EIB and pediatric patients were similar.

Note that the previously mentioned neuropsychiatric events are also as discussed in section 6.2 under psychiatric disorders. This section also includes labeling procedures. Additionally in the sponsors labeling, a section on renal and urinary disorders has been added which notes reports of enuresis in children.

I acknowledge the comments made during the public hearing on Singulair, and I have pointed out areas of labeling that discuss neuropsychiatric events because you will see in a moment that neuropsychiatric events comprise the majority of adverse events associated with Singulair. Therefore, I would like to provide you with a brief history regarding FDA's evaluation of

these events and association with montelukast use.

In 2008, FDA began reviewing FAERS data and clinical trial data to evaluate the potential association with leukotriene receptor antagonists. In March of that same year, FDA released an early safety drug communication which announced this review and an increase in reporting of events to FAERS was seen shortly thereafter. In August 2009, the aforementioned neuropsychiatric events subsection was added to the precaution section of labeling which is now the warnings and precautions section in the PLR format.

In this 2008 review, FAERS researched for events from February 1998 to March 2008 and revealed 400 adverse event. Half of the cases involved pediatric patients, and the most common reason for use was asthma. Of the multiple neuropsychiatric events reported, sleep disorders and disruptive behavior were the most commonly reported for all age groups. There was compelling data from the reports to conclude that some of the cases appeared to be consistent with the drug

effect, and you can see this language in labeling.

Now we'll turn our attention back to this current focus safety review for Singulair which reviewed data between March 2012, the date of the labeling change for EIB, and September 2013. Let's begin with use.

This figure provides the number of patients stratified by patient age who receive dispensed prescriptions for montelukast from US outpatient retail pharmacies from 2002 two 2013. Let me orient you to the slide. The overall number of patients increased from 3.5 million patients in 2002 to 7.4 million patients in 2007. It remained relatively steady thereafter. The number of pediatric patients aged 0 to 16 years increased to a peak of 3.1 million patients in 2007 before decreasing to 2.6 million patients in 2013. If you calculate, you can see that pediatric use ranged from thirty-six to forty-four percent of total use over the examined the time period.

We have seen how the use of montelukast

in pediatric patients changed over time in the previous slide. We now focus on pediatric use since the last pediatric labeling change in March 2012. This table provides the number of patients, stratified by patient age, who received dispensed prescriptions for montelukast. From March 2012 through September 2013, approximately 3.3 million pediatric patients aged 0 to 16 years received dispensed prescriptions for montelukast.

You can see again that total pediatric use has remained around thirty-eight percent. The highest proportion of these pediatric patients were age 6 to 11 years, at approximately forty-seven percent of the total pediatric patients. Pediatric patients age 2 to 5 years and 12 to 16 years followed at approximately twenty-nine percent and twenty-six percent respectively of total pediatric patients.

This next graph shows the top 10 specialties prescribing dispensed prescriptions for montelukast. Over the same time period, approximately 40.8 million montelukast

prescriptions were dispensed. Family practice/general practice/doctor of osteopathy accounted for the highest proportion of total dispensed prescriptions at thirty percent, followed by pediatricians at eighteen percent, an internal medicine t sixteen percent.

This next graph shows the top five diagnoses associated with montelukast use stratified by patient age. Over this same time period, asthma and allergic rhinitis were the two most common diagnoses associated with the use of montelukast for pediatric patients.

Now we'll turn our attention to safety and the pediatric-focused adverse events. You will notice that 570 or approximately thirty-eight percent of serious, adverse effects were reported in pediatric patients. Of the 75 deaths, 5 were reported in pediatric patients.

Now I will walk you through the case selection. Of the 570 total serious pediatric reports, we focused on the 162 events which reported an outcome of death, life- threatening

event, hospitalization, or disability which included five deaths. There were 21 duplicate reports, and one report was excluded because it was miscoded as a death. One-hundred-and-forty serious pediatric cases remain, involving four fatalities.

You will see that the demographics for the pediatric adverse events varied widely with respect to age and gender. In these next two slides, you'll see that the serious, adverse events were grouped into deaths, organ systems, general or administration site conditions, or miscellaneous events. The majority of cases involved psychiatric or nervous system disorders, and overall the adverse events were labeled.

I'm not going to discuss the labeled events and will instead focus on the fatal and the unlabeled serious events. First, I'll discuss the four events that involved fatalities. In the first event, a two-year-old male died of an unknown cause after experiencing recurrent episodes of fever, otalgia, and multiple

neuropsychiatric symptoms of which gait disturbance was the only unlabeled event. In the second case, the 16-year-old discontinued montelukast for unknown reasons after a three-year course for allergies and asthma and committed suicide the following day. No further information was provided for these two cases.

The third case involves a 12-year-old female with asthma and allergic rhinitis and no history of depression. She was switched to generic montelukast after taking Singulair for 3 to 4 years and developed behavioral and sleep changes. Poor compliance was noted. Despite various changes to her treatment regimen, including restarting and later stopping brand Singulair, her symptoms persisted and she committed suicide 4 months after the onset of her symptoms.

In the final case, a nine-year-old male with no history of depression or mood disorders had been taking montelukast alone and died from an apparently self-inflicted gunshot wound. Whether

his actions were intentional or an accident is unclear due to the lack of information.

To summarize, there is one case where the cause of death is unknown, and as you can see, with the exception of gait disturbance, the remaining neuropsychiatric adverse events are labeled in the warning and precautions section. Furthermore, limited information is provided in order to assess causality.

Now let's discuss the nonfatal unlabeled events. As we go through the cases, you will notice that the majority involve the single events, and many include confounding factors or provide insufficient data thereby limiting determination of causality.

There were 11 psychiatric unlabeled events. Six of these cases report obsessive compulsive disorder and psychotic disorder. Of the six cases, a positive rechallenge was noted in three. Two cases of Tourette's disorder are reported without further information.

In an additional case, a two-year-old

reportedly developed motor tics 4 to 5 months after starting montelukast and discontinued use 6 years later with a decrease in symptoms. Also, a seven-year-old developed excessive eye blinking with a positive rechallenge. In the final unlabeled psychiatric case, a three-year-old female began to exhibit abnormal behavior of crying and wanting to be a baby again, which resolved 4 days after discontinuation of montelukast. In these psychiatric events, insufficient data was provided to determine causality.

Five cases involving nervous system disorders were identified, all of which were single events. A four-year- old developed knee pain 7 years after starting montelukast that progressed into an inability to walk over the next four years. Note that labeling for Singulair includes arthralgias and myalgia.

A 12-year-old female experienced recurrent symptoms of loss of consciousness, bradycardia, and pallor within 10 minutes of

montelukast use, suggestive of a hypersensitivity reaction which ultimately resulted in cardiac resuscitation.

In one foreign report, the 15-year-old was diagnosed with neural vegetative dystonia with marked psychosomatic signs and peripheral vestibular syndrome after experiencing nausea and vertigo on montelukast.

There was an isolated report of an eight-year-old on multiple medications that developed elevated intracranial pressure, and finally a seven-year-old with asthma on multiple medications that developed a speech disorder and gait disturbance. In all these single neurologic cases limited information was provided for proper assessment of causality.

Seven cases identified general events including four cases with worsening asthma or bronchiolitis symptoms after switching to a generic formulation, one case with an unspecified event, one case where montelukast was reported to be ineffective for the treatment of asthma, and

finally one case of a 13-year-old female with food allergies who developed lip swelling 30 minutes after taking cetirizine. She was also taking montelukast, and note that both cetirizine and montelukast contain lactose. Causality cannot be determined because many patients were on concomitant medications or had insufficient clinical data.

Two cases involved isolated events of immune system disorders. In both cases, patients were taking multiple medications and were on montelukast for an unknown duration. One patient developed exfoliative dermatitis, and the other developed systemic lupus erythematosis.

There are five cases involving respiratory thoracic or mediastinal disorders. Two patients were hospitalized for respiratory failure, and one was hospitalized for obstructive airways disorder. In one case, symptoms occurred four hours after receiving a varicella vaccination, and the other two cases were associated with an asthma exacerbation.

In one case, a seven-month-old with an upper respiratory infection developed apnea after aspirating montelukast granules which were being administered to treat asthma. There was also one case in which a nine-month-old was taking montelukast for obstructive bronchitis developed pulmonary tuberculosis along with his three siblings. Of note, the other three siblings were not taking montelukast.

Many of these respiratory cases can be attributed to the underlying disease state or are confounded by concomitant exposures and treatments.

The two gastrointestinal cases involved a five- year-old with asthma and anemia on multiple medications that developed celiac disease after an unknown duration of montelukast therapy and a 24-month-old that developed C diff colitis. No further information was available.

In the single case involving skin and subcutaneous disorders, a 12-week-old was started on montelukast for RSV and developed loss of hair

from his head, erythroderma, and easily denuded skin in the diaper area. Further information such as timed onset or outcome of the event was not provided to determine the relationship between his symptoms and montelukast.

A couple miscellaneous events were reported. The first involved an 11-year-old who was taking montelukast and budesonide for asthma that developed visual disturbance and a headache that required hospitalization. No further information was provided.

In the second, a four-year-old female on multiple medications developed a headache, language disorder, and fell two months after starting montelukast. A cerebral CT was normal and montelukast was discontinued. The patient recovered from the events. Again, however, information was limited, and the patient was taking other medications that could be associated with the events.

Three single events involving vascular disorders were reported. In one case, a

two-year-old female with a history of multiple respiratory infections, adeno-tonsillar hypertrophy, and bilateral serous otitis underwent two otolaryngology surgeries complicated by infection with the first surgery and recurrent hemorrhage with the second. She had received multiple antibiotics, varying inhaled steroids, and albuterol. A family history of coagulation disorders was noted and was also suspected in this patient. However, the hematologic evaluation was incomplete.

In the other two single vascular events, one patient on multiple medications developed a hematoma with decreased platelet adhesiveness, and the other developed Henoch-Schonlein Purpura with diffuse joint swelling. In both cases, limited data was provided and outcome was unknown.

There were two cases identified involving blood and lymphatic system disorders. In the first case, a 10- year-old male on multiple medications, including pimecrolimus cream for an atopic dermatitis study, developed Burkitt's

lymphoma. In a second case, a five-year-old male was diagnosed with leukemia 2 years after starting montelukast for asthma. Montelukast was discontinued. Following treatment, both patients' malignancies improved. Due to insufficient clinical information and concomitant medications, the role of montelukast could not be determined in these cases.

Two cases of tachycardia resulting in hospitalization were identified. However, the patients were on multiple medications and limited clinical information, including duration of montelukast use, was provided to assess causality.

The final unlabeled event involved in eight-year- old female that developed type I diabetes mellitus one month after starting montelukast. She was also taking cetirizine which is labeled for diabetes. No other information was provided.

This concludes the pediatric-focused safety review. As a result of the studies conducted under PREA, labeling has been updated to

expand the EIB indication to patients 6 years and older. In summary, many of these events involve single cases, had confounding factors, or provided limited information from which to draw causality. No new pediatric signals were identified, and the FDA recommends ongoing surveillance be continued. We also ask if the committee concurs. I'd also like to acknowledge the folks on this slide. Thank you.

CHAIRMAN TOWBIN: Thank you very much, Dr. Radden. Just to underscore that Dr. Cataletto has stepped away from the table for a discussion of montelukast or Singulair. Comments or questions from people? Ms. Celento?

MS. CELENTO: Yes, I just want to reference the label. In the warnings and precautions section, bullet number five, neuropsychiatric events, I will say that if you survey most Americans, they don't even know what the term neuropsychiatric means. This is the kind of thing that, when it ends up in a label and it's a warning and precaution, it's just whitewashed.

I really want to stress the point that there needs to be a clarification around neuropsychiatric, and also when you reference a subsequent section of the label with just the number in parentheses, most people don't understand that you're saying see section 5.6 below or section 5.4, whatever. I understand that FDA doesn't own the label, but the manufacturer does, and they really need to be addressing this.

We can't have people making presentations about the trauma their children have suffered because the parents were completely unaware. Most people aren't going to read a whole label, but they may pay attention to a warnings and precautions section if it's carefully worded. Thank you.

CHAIRMAN TOWBIN: Dr. Nykanen?

DR. NYKANEN: I would agree. I think that one of the things concerning to me as I'm listening to this is that most of the side effects that we're seeing, first of all, they're relatively less common or relatively uncommon, but

the thing that I find different about this is you have the drugs that you're using to treat asthma and you're having a side effect that has neuropsychiatric implications.

What I'm more concerned about is the disconnect. It's there. All that information is there, but the signal- to-noise ratio is such that it just doesn't hit. I'm pretty sure that if I went to my pediatric pulmonologists and ask them, they might say, 'Yeah, maybe there is some association,' but this is the kind of thing that may be underreported.

We had a similar conversation at one of our previous meetings with a smoking-cessation drug, and we were all very concerned because it had a psychiatric component it. We said we want to make sure we continue to track that. We are tracking this, and everybody knows that with smoking- cessation drugs there can be a psychiatric impact to that.

I think where I'm having difficulties here is that even out in practice I think the

awareness that there may be a neuropsychiatric component where there may be a problem associated with behavior or a problem associated with the autonomic nervous system, we may not be picking up the signal because of not looking for. I think the surveillance is very appropriate. The surveillance that's been going on is very appropriate, but I wonder if there is some way through MedWatch or some way that -- I'm sure the people who work for the FDA are much better versed than I am -- we can increase the awareness so that we can understand what the numerator is for this.

CHAIRMAN TOWBIN: Dr. Mink and then Dr. Dracker.

DR. MINK: I think the presentation and review of this points out something we've discussed on this committee before, and that is the difficulty. It was brought up before too, the difficulty with labeling these different adverse events.

I'm a dystonia expert. I spend my career studying dystonia. I never heard the term

neurovegetative dystonia ever. I had to look it up. Apparently it's used a lot in Brazil, but I had no idea what that is. Then when we look at the laundry list of neuropsychiatric complaints, and we see there's one of this and there's one of that and then a couple of that, it suggests that you can pick it apart and say there's no big signal there. But clearly if you put all of these things together into broader categories -- emotional changes, mood changes, etc -- it becomes more significant.

I concur with the concern about labeling these neuropsychiatric without further elaboration, but I also have the same concern about having this microscopic view, including terminology that not even experts in the field recognize as acceptable terminology.

CHAIRMAN TOWBIN: Dr. Dracker and then Dr. Rosenthal.

DR. DRACKER: I just wanted to first mention that despite these events that children have experienced, that I've seen myself that have

not been persistent in nature once they've stopped the medication, but I have seen it in my practice. But I've been a very strong advocate of Singulair as well as montelukast for patients with reactive airway disease who its helped quite a bit and also patients that have severe infliximab reactions, immediate reactions. It's worked very well for that.

Despite that, I looked into why it might be causing a CNS issue. The reason I looked into it is actually I studied it when I was a resident looking at this whole pathway and platelets unfortunately. It was unpleasant, but I did it anyway. Regardless, apparently there is an issue with regards to DNA methylation and lipoxygenase metabolism in the brain and leukotriene formation. It's only affected a very small group of individuals, and there is a small call for epigenetic studies in some patients to see if they are at risk for neurologic sequelle related to leukotriene inhibitors.

I think it's something that we should

monitor, and we've talked about this before as well, and that is to remind physicians to do a better job reporting when they see side effects from medications to our patients and not just minimize complaints or experience the parents have with their children. Saying, it's just your kid. He'll grow old and develop a psychiatric problem, and we'll deal with that. It may be real and may be related to medicine, but they need to get us the information.

CHAIRMAN TOWBIN: Dr. Rosenthal?

DR. ROSENTHAL: I first have a question. I may have missed it because I was looking at Tamiflu and something about the Tamiflu discussion from many years ago, but is there an age-dependent relationship or does there seem to be to the reporting of these neuropsych symptoms?

CHAIRMAN TOWBIN: Dr. Radden, would you have a common about that or would somebody from FDA?

DR. KALRA: Yes, I could speak to that.

CHAIRMAN TOWBIN: Who are you if you

don't --

DR. KALRA: Dipti Kalra, safety evaluator --

CHAIRMAN TOWBIN: Thank you.

DR. KALRA: -- Office of (inaudible). Looking at the Ferris cases, most of the neuropsych events were between the age of 7 to less than 17 years of age, that was the group that we saw. We also looked at adults, and most of the reports for 17 to less than 65 years of age.

DR. ROSENTHAL: One of the things that I was remembering -- my wife will happily tell anyone in the room that I usually misremember, so correct me if I'm not remembering this correctly, but in the Tamiflu discussions one of the things that came up before the warnings are strengthened related to Tamiflu and kids. There was an unusual pattern of behavior; there were a few kids who were caught around windows are outside of windows and tall buildings. It was specific enough and an unusual enough situation that it really grabbed everyone's attention, and it was the specificity

that, I think, that drove to some extent the Committee's interest in strengthening the warnings.

In this case, to Dr. Mink's point, it doesn't seem to be the specificity around the exact story, but there does seem to be some specificity around the class of AEs that are reported for this agent to what seems to me to be an equally noteworthy extent.

CHAIRMAN TOWBIN: Dr. White?

DR. WHITE: Michael White. I'm going to play the devil's advocate because A) reporting goes up once it gets out that there's a problem, and it's obvious that people think there's a problem, and there may be. I can't prove it one way or the other, but I'm going to leave it to Dr. Towbin and Dr. Mink to answer my question which is what is the incidence of neuropsychiatric problems in this age group, and is it significantly different from what we're seeing here where we've got 80 reports in 3.3 million patients taking this drug?

It's going to be really hard to sort out the signal-to-noise ratio here. If we look at this statistically, we don't have a statistically significant sample. If you look at the incidence of neuropsychiatric problems in children between the ages of 6 and 17, where the predominance of the reports are, that's when they start showing up. I believe that's correct. You guys are the experts, so I'm (inaudible) you.

CHAIRMAN TOWBIN: Dr. Mink would like to answer. I'm happy to follow up.

DR. MINK: Maybe you can follow up too. Certainly the incidence and prevalence of this group of disorders in this age range is substantially higher than you would expect based on the numerator and denominator we're talking. What makes these different and concerning to me is at least of the individual descriptions we've gotten, it sounds like they're acute in onset, some of them go away with (inaudible) medication. It's very hard to tell from the information how many do, but to have an acute onset is, in my

mind, different from a more insidious onset which is a little more common in most of these disorders.

DR. WHITE: But if you look at some of the reports, the kids have been taking it for a while, and they are also taking confounding drugs at the same time. Many of them are taking steroids which have neuropsychiatric --

CHAIRMAN TOWBIN: That may speak to the way I was going to answer your question, if you don't mind.

I think that the more specific question you're asking is what is the rate of these kinds of mood, behavioral, and thinking problems in children with asthma who are the most likely population (inaudible) because these kinds of psychiatric problems are very common in children who have relatively refractory asthma just as many chronic pediatric illnesses seem to engender these kinds of psychological or psychiatric difficulty. The rate for all of those increases in children with chronic medical conditions. Respiratory

conditions are not an exception to that.

I think that the review that came up for the nonprescription advisory committee when this was looked at for another reason really pointed to the absence of information that we have. We really don't have good data, and so the problem here is that you're trying to distill from this rather limited data whether there's a signal in there. Dr. Mink, I think, very correctly points out that acute onset of these kinds of problems in children in this older age group and also the challenge, rapid reduction in symptoms, in some cases even report of rechallenge causing the symptoms again, that leaves one uneasy.

You're right; when we see a case report of someone who's been on a drug for 7 years and then suddenly develops problems with mood or problems with behavior we might think about other kinds of etiologies when that's a stable dose. But I don't think that you can dismiss all of these either, and so at least what I was left with when we were reviewing this rather recently is we

just don't know.

The Committee wants to advise FDA about what they need to say or how we need to proceed, but I don't think that we can get better data by what we've got so far. I just don't think that will give us what we need.

DR. WHITE: That's, kind of, what I'm trying to get to; not that I really believe the opposite. How do we get better data?

DR. MINK: This is John Mink again. If I can just follow up. I agree with you completely that we just don't know, and for each one of those specific patient examples that was given, I can find other explanations. It's the number that makes me concerned out of proportion to other things like the usual upper respiratory infection and bruising or whatever else. The preponderance of the reported adverse events that are in this broad category of mood, behavior, thinking problems, which I think are far better terms than neuropsychiatric --

CHAIRMAN TOWBIN: I often have to

translate this for people.

DR. MINK: -- again makes me concerned that we don't really know if this is truly a causal relationship.

CHAIRMAN TOWBIN: Dr. Yang?

DR. YANG: I just wanted to piggyback on what Dr. Towbin was stating. I just want to provide some comments and then maybe rephrase and ask the Committee.

First of all, I just wanted to make the distinction between physician labeling and patient counseling information. I would wholeheartedly agree with Ms. Celento's description of neuropsychiatric events and then the, sort of, laundry list of things that flow from that as being, sort of, jargon and not necessarily very granular in terms of what we really think is going on, and that's in physician labeling, so this is prescriber labeling. We hope that alerts prescribers to this collection of very -- may be hard to connect, but that clearly we believe fall into this category.

If you scroll down to the end of the label, I'll direct your attention to patient counseling information. Under that, there's a whole section that says Singulair may cause serious side effects, and it talks about behavior and mood-related changes. It goes through what, I think, is a list of things and hopefully are in more patient-friendly language that describe agitation, aggressiveness, behavior, attention problems, bad or vivid dreams. So, I hope that that speaks somewhat to trying to get the information out to patients.

Now having said that, one of the things that I hope Dr. Radden's presentation highlighted was that we may not ever get to we know that this mechanism causes this change, causes this behavior. I'm not sure that we need to because I think what we need to do is alert prescribers and patients, and I think we've heard very compelling testimony that there are still patients out there who don't know that these are potential problems.

We sent out a drug safety communication

in 2008. We put this in warnings and precautions. What I think would be helpful to FDA would be to tell us how else can we communicate this information. I think that's what I heard in the testimony. Is there more that we can be doing as FDA, as advisory committee, to communicate that this is a problem or that we've seen it? It's in labeling already.

My first question is what can we do? Can you give us advice about how we should be reaching out in communicating number one, and number two is there really other data that we believe needs to be collected before we communicate additional information?

CHAIRMAN TOWBIN: Yes, Dr. Nykanen?

DR. NYKANEN: I don't know how the politics of all this works, but is there a mechanism wherein -- I'm sure that there are groups like the American Academy of Pediatrics, pulmonology societies that work with the FDA on these types of issues -- getting that information back to society saying that the Pediatric Advisory

Committee had this concern that there was a disconnect in this drug.

There's the signal here that we've spent the last 15, 20 minutes talking about, so it's got to be real. No matter what we think about it, it's enough that it's got our attention. Having that conversation back with those societies, not necessarily to suggest we need a study but to get the information, the physicians doing the work and the researchers doing the work and the pulmonologists that are interested in this are obviously very interested in if their drug is causing side effects. They'll do the work. They'll do a lot of that work and put those things together because if it's an important thing they will do it.

I guess what I'm asking is is it an appropriate means? We talked about this in Pediatric Infectious Diseases earlier with the Levaquin. Is there a role for the communication? I'm naove; I don't know if that already exists and exists in a big way, but maybe there are some

things that come out of this meeting that should come across as being, sort of, highlight, pressure point kind of thing so that we can get rid of the noise and focus on the signal. We've had a daylong meeting, and we spent a long time talking about this, so it is the kind of thing that we all believe is important.

CHAIRMAN TOWBIN: Dr. Nelson, did you want to say something?

DR. NELSON: I agree with Lynne that it would be helpful, and some of the things that one could consider, there's various communications that FDA can make. Health safety communication, different processes by which if a signal was of concern that that can be released, and then that would be picked up by professional organizations and so on and so forth, so that's one mechanism.

The other would be a question of whether or not you believe the risk-benefit evaluation that a clinician would go through as an appropriate balance within the label itself and other things that ought to be elevated in terms of

the level of concern that it raises. Those are some of the questions that I think you could legitimately provide some advice because these are in the label and they are there, but what we've heard is that it just doesn't seem to be reaching that level of concern that people think might be appropriate. Can the label be changed to do that? Limited impact, but it's something, or other communications that we could make?

DR. NYKANEN: Maybe then -- if I could?

CHAIRMAN TOWBIN: Go ahead, Dr. Nykanen.

DR. NYKANEN: I'll use the follow up since I trailed on my last line. One of the things that I noticed in the label as I was trying to figure out signal-to-noise as I'm reading the label is the label says that if your child, your patient, experiences these problems, give consideration as to risk-benefit associated with going through. Maybe it needs to be stronger than that. Maybe it needs to be considered very strongly stopping the medication; assessing the behavior, and then terminating if the risk-benefit

is there.

As a physician, when I figure out if the risk- benefit is there, if I'm not even aware that's on the list or may or may not be involved in aggressive behavior, it's, okay, well, a 12-year-old gets aggressive. On the other hand, if the label says, 'If child's behavior changes, give very serious consideration to stopping the drug, reassess, and then determining if the drug is going to hell.'

Nobody's going to be hurt from a month off the drug, and if their behavior changes it sure is going to raise my awareness that he developed this aggressive behavior or this mood disorder on the drug, and then I stopped drug, and it went away. Boy, that sure makes me think that the drug in the behavior are related. That increases my awareness, changes my behavior, and may help the patient.

CHAIRMAN TOWBIN: Dr. Reed, did you want to say something? Then Dr. Wiefling.

DR. REED: Yeah, Michael Reed. David

touched on what I was going to say in response to Skip and Lynne's comments.

Yes, I think there's a clear disconnect here. Looking at the warnings and precautions, I think we're saying all the right things, but we're not getting that across. If you read the statement in label, as you just said, 'Neuropsychiatric events have been reported. Instruct patients to be alert for neuropsychiatric events.' If that terminology is not common to a lot, I think we need to spell out some things that better highlights the magnitude of what we're talking about.

If you look at systemic eosinophilia, and we comment that sometimes that presents with clinical features of avascularitis gives a greater magnitude of what that is where we could be just modifying that statement somewhat to state, 'Dramatic changes in behavior including,' even if you said suicidal ideation, which is seen here, I think that would send a message a lot more clearly in that section be of much greater benefit to the

prescriber in putting some of this into perspective.

CHAIRMAN TOWBIN: Dr. Wiefling, and then Dr. White. Please.

DR. WIEFLING: Thanks. This is Bridgette Wiefling. Normally I'm all over bad labeling, but the patient section on this one is pretty good, and it's pretty clear that it says tell your doctor if you're experiencing any of these, and it is very much in lay language. I can't pick it apart from that perspective, and it does use suicidal thoughts as one of the things that's listed, so I think we're getting back to the issue of just public awareness.

It seems to me that I remember a few years back we had a similar situation, and I don't want to say the drug that I believe that it was in, but we did just a provider update information letter that we had sent out, like a 'beware of this' kind of thing. I'm just wondering if that -- not a black box wording because I think we're not there yet it all on any of that stuff, but

just something that says, hey, you guys might want to take a look at this as providers because we're starting to see some of these. I guess I'm questioning does it raise to that level at this point.

CHAIRMAN TOWBIN: People may want to actually weigh in on that or maybe thing about it. Dr. White?

DR. WHITE: Michael White. I think Dr. Nykanen's comments were quite helpful, and I think Dr. Nelson as well. I don't think that you can send out a black box warning and say, don't give this drug. We're nowhere near that, but is there -- and it sounds like maybe you've done this before -- you send out some letter to practicing physicians (inaudible) family practice and pediatrics as well because a lot of kids are taken care of my family practitioners just to state that if you observe these things in your patients or your families come to you, you should consider a trial off medication to see if the symptoms change in any significant way and give some advice for

how to proceed. Not just be aware of it, but maybe we should proceed with a trial off medication to see if the symptoms resolve or the behaviors change.

I don't know how that can be accomplished. I don't know what the authority of this Committee is to have things like that sent out to people.

DR. MURPHY: We did that.

DR. WHITE: We did that? What did we did?

CHAIRMAN TOWBIN: Go ahead, Dr. Nelson.

DR. NELSON: I always deal with primary data, so I'm going to look at it myself, although I believe (inaudible).

CHAIRMAN TOWBIN: Thank you. No, that's fine.

DR. NELSON: Basically the information I'm told is that the letter that we sent out in 2009 says that you ought to consider discontinuing the therapy.

DR. WHITE: Apparently didn't help, did

it?

DR. YAO: I think that the question really is not that we did it. I think the question is is I think that we heard that we did it, and Dr. (inaudible) points out that we were very quick to send out a drug safety communication which is our way; wrap up communication and get it out. That was done, and we did send out dear healthcare provider letters, and that's been 5 years. I think maybe people have forgotten that.

DR. WHITE: Yes, (inaudible).

DR. YAO: There are new providers too, so I'm not saying that that didn't work. I'm just saying that maybe it did work. I was struck by the use data that presented in one of the slides that from the peak in 2008 you see it actually come down, and it seems to be correlated, temporarily, with that communication. But it's been pretty flat, so is there a need then to reiterate something from 5 years ago? That's really the question, I suppose, we're asking.

DR. RADDEN: This is Dr. Radden.

Reporting increased after the drug safety communication as well.

CHAIRMAN TOWBIN: I'm sorry?

DR. RADDEN: Reporting increased after that drug safety communication.

CHAIRMAN TOWBIN: I bet that's true, Dr. Radden. Thank you for that. Dr. Cunningham?

DR. CUNNINGHAM: Sure, Melody Cunningham. I agree that the information in the labeling is appropriate, but it's very difficult in its formatting to find what you need to find, and there's all kinds of information about the dosing in different age groups which ought to be on the prescriptions that are given to the patient from the doctor and ought to be clearly given in the office, clearly given on the prescription. They have all of that information, and then you drop down to questions about safety issues.

I think even a formatting of this information that ought to be straightforward -- given in the office, given on the prescription -- not be very high on the labeling, but if they were

asked to move the safety information up to the top and then format such that -- really, if you look at it, it all lines up on the left. It sounds silly, but it does make it difficult to pull out what you need.

CHAIRMAN TOWBIN: Dr. Rosenthal, then Dr. White.

DR. ROSENTHAL: I was getting confused with the label as well. If you go to the end of what looks like the label -- on my PDF it's down on page 2425 -- it's in a section that's specifically for the patient. I think that's the area where it's really very clear, and I just wanted to reiterate Dr. Wiefling's comments that the language that's used, the way that it's laid out, it says, 'Singulair may have serious side effects' and then bullet number one is behavior and mood-related changes. Then there are a number of bullets underneath that that are, I think, in language that people will understand.

CHAIRMAN TOWBIN: Dr. Mink?

DR. MINK: Could that language be

replicated above in what the physicians read because a lot of physicians don't read the patient information.

CHAIRMAN TOWBIN: Dr. Nelson, why don't --

DR. NELSON: I'd like to ask a concrete question. This label happens to be in the new labeling format with the highlight section at the top. On the assumption that physicians may want to read the Cliff notes version and may not read the entire document, the concrete question would be if looking at the warning and precautions section in the highlights, whether the three sentences that are there could be improved specifically to highlight this concern, and how one might improve those sentences? I don't want to put words in your mouth, but I guess that's where one could focus.

CHAIRMAN TOWBIN: No, I think your questions are always useful to us, Skip. That's not a concern. One thing is maybe we want to remove fancy words like neuropsychiatric because

one of the things that ties Dr. Mink's comments and mine together is we don't really believe that problems in gait and disturbances in speech and cognition come from a different organ than the ones that relate to mood and behavior. Maybe instead of neuropsychiatric, we want to talk about mood, behavior, and thinking. Those kinds of things might tie those together.

DR. NELSON: If I may make an analogy, I sometimes said in my previous life as an (inaudible), you do a child a (inaudible) that's often better to be used for the parents because it's more understandable. What I hear you suggesting is what we've developed for the patient information and counseling information might be better for the physicians.

CHAIRMAN TOWBIN: It would be really good if they agreed. I think that --

DR. NELSON: That's, kind of, what I'm hearing.

CHAIRMAN TOWBIN: Yeah, I think that's right. Ms. Celento?

MS. CELENTO: Amy Celento. To Skip's point, are you talking to a sixth grader? That's, kind of, the level that you want to go for for a form of consent; it's the same kind of thing here.

CHAIRMAN TOWBIN: Right. I think that's exactly right. Dr. White?

DR. WHITE: I almost forgot. This is a regulatory thing, and I need help with it. The label belongs to the company. Is there anyplace at our website where we could put up what's at the end of that label as patients looking for information on Singulair, can patients go there and get that summary of patient information independent of the label? I don't think families really look at the label very often, but if families are aware that there's a problem with the drug, and they're going to be aware of that, is there someplace we can make that easily available to them? Do we have the facility to do that?

CHAIRMAN TOWBIN: Dr. Nelson?

DR. NELSON: If you go to your pharmacy and get a prescription, there is a printout that

comes with it. I'm assuming --

CHAIRMAN TOWBIN: That's what they get.

DR. NELSON: -- that they get the patient information, that that printout may be modified by the particular vendor, but it would include the information that's in the patient counseling form, not the label.

DR. WHITE: Right. Do you read that?

DR. NELSON: Yeah.

DR. WHITE: When you get it?

DR. NELSON: The first time I get a new drug from my doctor I do read it, yes. But whether there'd be any chance of reading that less than you would go to a website, I guess, is an open question.

CHAIRMAN TOWBIN: Ms. Celento?

MS. CELENTO: Amy Celento. I want to make a comment to what you're saying, skip. It depends on how old you are. Honestly, if you're probably somewhere 15 to 27, you don't read anything on a piece of paper. You look it up. You get out your phone, that's it. You don't read

anything someone hands you. I think we have to look at that as, to the point, I think, Michael White made, is there something on a website? Is there a way to have a summary? People look to YouTube to find out information. They don't look to a piece of paper.

CHAIRMAN TOWBIN: Dr. Nykanen, did you want to make a comment here? Then Dr. Reed.

DR. NYKANEN: Sure. I think in addition to your comments, just thinking about concrete things that can be done on the label, my suggestion would be that in the warnings and precautions area that we make some of the adjustments to the term neuropsychiatric as you suggested. Instead of saying evaluate the risks and benefits of continuing treatment, I would say consider strongly discontinuing treatment, reevaluating the patient, and determining if the risks outweigh the benefit in the event that these things occur.

Thirdly, to maybe have another dear practitioner type of letter, and fourthly to maybe

communicate with some of the societies that this has hit our radar because then maybe they'll go back, and you get a cross pollination. Those would be four concrete things that I could think of.

CHAIRMAN TOWBIN: Dr. Reed?

DR. REED: Michael Reed. Actually David touched on the two things that I was going to say. I had articulated earlier about the warnings and precautions section. I do believe it needs to be modified. I do believe it needs to be strengthened relative to the serious risks associated with that. I think that will get attention. I also do believe that it's also time to send out a reminder letter. Different time, different place.

CHAIRMAN TOWBIN: Dr. Hudak, and then Dr. Cunningham.

DR. HUDAK: I think I agree in principle with most of the comments about improving the clarity of the labeling. I think the essentials are there, but the clarity can be improved.

I do have a question though. I do think that all of these cases -- there were 224 deescalated and 24 rechallenges for 260 or something cases in FAERS where there seemed to be a clearer connection between drug and effect. This sounds like a really good project for someone in NIH to do epigenetic analysis of these children. Is there a mechanism to make that happen or to initiate some project? I think it would be really fascinating if you had a bunch of these children -- to have blood and look at it and say, okay, can we identify a common factor that puts these children at risk and then do a mechanistic investigation, getting to the point of the presenter that perhaps some of these children could be identified as being at higher risk ahead of time? I think that would be a fascinating scientific study, and it's where medicine is going.

CHAIRMAN TOWBIN: Dr. Nelson?

DR. NELSON: You would need a repository of blood at the very least, and then a large

clinical data set that would include some of these adverse events. The question would be who might have that?

DR. HUDAK: This would be in the arena of -- the AAP sponsors a pediatric, sort of, office-space trials network. This would be the sort of thing if you had practitioners aware that they have this issue that they could report some history. (inaudible) the parents to draw some blood or things and have a nationwide sampling.

DR. NELSON: Just (inaudible) need to run the samples, so --

DR. HUDAK: Right, yeah.

CHAIRMAN TOWBIN: Dr. Cunningham?

DR. CUNNINGHAM: Sure. Melody Cunningham. I guess I'm sticking on this point. Even on page 24, I agree with you that the information is clear. I don't think that it's laid out very clear, and it's well below the information that says for this age group this is the dosing, for this age this is the dosing, which is really, to me, superfluous for patient

information because they've gotten that in another way. I think to recommend bringing the information from page 24 higher up to the patient information actually would make it more accessible to the families.

CHAIRMAN TOWBIN: Dr. Wiefling and then I think Dr. Mink or Dr. White, but I do want to begin to wrap this up a bit. Dr. Wiefling, please.

DR. WIEFLING: Just a practical note. When we send a letter out I think the other thing is that if you want to make that change to the labeling, make sure you let UpToDate know because I think that's where most of the doctors get it from. It's clearly there from the label, but if you're going to make recommendations about changing it I would make sure they get it.

The other thing is when you use the FDA access site for the label, it's the old label format; it's not the new label format, so that's another thing you just might want to check into.

CHAIRMAN TOWBIN: Good. The duo there

of Dr. Mink and Dr. White, which of the two of you was going to speak next?

DR. MINK: I think we simultaneously went to our friend, Dr. Google, and searched for Singulair side effects.

DR. WHITE: We did. What was yours that came up?

DR. MINK: I came up with the MedLinePlus drug information that's published by the National Library of Medicine in conjunction with the American Society Health- System Pharmacists. Under side effects they list: Headache, dizziness, heart burn, stomach pain, tiredness, difficulty breathing, swelling, hoarseness, itching, rash, and pain. Then they say, 'May cause other side effects. Call your doctor if you have unusual problems.'

There's another section: What special precautions should I follow? Then there's a paragraph, 'You should know that your mental health may change in unexpected ways while you're taking this medicine.' That's one source of

information, and that is the same federal government that is sponsoring this meeting that's providing something that is very different from what is on the patient information on the packages.

CHAIRMAN TOWBIN: I suspect that NLM, the National Library of Medicine, probably didn't consult with the FDA about how to go about doing that, although I'm not quite sure how MedLinePlus gets to what it does. There's also a thing called DailyMed that's also National Library of Medicine, and I bet that would have a different kind of listing.

DR. WHITE: I got everydayhealth.com which has nothing to do with anything we do. It says, 'Call your doctor at once if you have a serious side effect such as: Skin rash, bruising, severe tingling, numbness, pain, muscle weakness, number 2, mood or behavior changes, anxiety, depression, or thoughts about suicide or hurting yourself.' It's out there, and apparently you can find it on your phone in a heartbeat. That's the

very first thing that came up when I put in Singulair side effects.

CHAIRMAN TOWBIN: Its in everyday parlance.

DR. WHITE: Yeah. It seems as though our best bet is really just going to be to send that letter out again and --

CHAIRMAN TOWBIN: Let me see if I can make a statement that will weave these together, and I do think we're probably looking at a couple of votes on this.

If I'm grasping the will of the people accurately here, I think that there are concerns about the labeling. I think people would like to have more plain language in their concerns, particularly problems in mood, thinking, and behavior fall in the consumer information. That is, the format and the way that they're presented doesn't make for an easy finding of those. We think these are pretty important side effects for people to know about.

If such a change were made that there

might be a subsequent letter that would go out that would remind people about these, perhaps using the change in this consumer information as a basis for sending a letter out just so that it's more highlighted for people. It sounds as if that certainly could be accomplished.

I think Dr. Nelson's question about how to reach out might be answered by that recommendation from this Committee. There's enough of a consensus here, I'm hearing, that people would like those two things to be different.

As to how to get better data, I think that we don't have a uniform voice, but we're speaking about that. I do think that there is a uniform wish that we had a better sense than the AER system to begin to get the information about the frequency of these kinds of events. I don't think that we've come up with a really great recommendation for how to go about doing that, but I do think that we certainly would wish that we could have that.

If there was an opportunity as you have discussions with the Heart, Blood, and Lung Institute or NICHD or anybody -- I do think NIH is probably the right place to begin to think about this kind of problem. I do think these are matters of pretty profound public health that have people concerned. Maybe even NIMH, but I think those other institutes are more likely to be the ones that are going to be looking at these kinds of problems.

I think this first thing, if I can just frame something that we might vote on, is that we would request that there be a review of the labeling, particularly the consumer information available with an eye toward formatting in particular. Based on that, there would also be secondarily a letter that would be sent out to providers informing them about some of these changes and concerns that families be reminded about side effects from this particular agent. Dr. Nelson?

DR. NELSON: Let me just ask for

clarification because --

CHAIRMAN TOWBIN: Sure.

DR. NELSON: -- what I heard, specifically the prescriber labeling information was not nuanced enough in terms of neuropsychiatric as far as the jargon there. The comment about consumer information was that it was there but perhaps it was there later than it ought to be. That it might be better to be higher up in the consumer information so you get there first instead of getting it after the dosing, but that actually the way that it described in the consumer information was pretty good. Is that --

CHAIRMAN TOWBIN: That is correct. Actually this is a (inaudible) question. I was going to say does the sponsor also own that consumer information? I know they do the label for the drug itself.

DR. NELSON: I don't know that question, but basically if they're safety labeling the FDA has much more jurisdiction over safety labeling than it might over kinds of labels.

CHAIRMAN TOWBIN: Then my sense was that the group really wanted what was in the label to agree with what has been put in put in effect.

DR. NELSON: Right. We can work out what authority we have, but we'll make every effort to do it.

CHAIRMAN TOWBIN: Okay, thank you.

DR. REED: Dr. Towbin, I think there was more consensus of the consumer labeling being rather strong, straightforward.

CHAIRMAN TOWBIN: Clear.

DR. REED: Skip brought up that the professional labeling needed the tweaking. I would just modify your comment to that.

CHAIRMAN TOWBIN: All right. I'll try one more time. Dr. Rosenthal?

DR. ROSENTHAL: Specifically I think that Dr. Nelson's point, the warnings and precautions, which is in the main part of the label, is an area that seems to be of opportunity for strengthening that (inaudible).

CHAIRMAN TOWBIN: All right. The three

recommendations, thank you very much for assisting me. I'll get there eventually. The first is that the label itself should have the same kind of clarity and transparency that we see in the consumer labeling. That people would like to see the consumer labeling formatted in a way that it's easier and actually comes higher up in the identification of things for people to be aware of, and that with these changes that there would be a letter sent out to providers so they're aware of these changes. Did I get that? I'm seeing nods. All right.

I think we should vote on that, and we'll talk about the question. Can I see a show of hands of people who would agree with those as what the Committee would recommend? Good. Anybody disagree? No, okay. Dr. Wiefling, if you'll help us?

DR. WIEFLING: This is Dr. Bridgette Wiefling, and I concur.

DR. YANG: Lynda Yang. I agree.

DR. MINK: Jon Mink. I think this has

been very useful, and I concur.

DR. WHITE: Michael White. I agree.

DR. BAKER: Susan Baker. I agree.

DR. DRACKER: Bob Dracker. I agree.

MS. CELENTO: Amy Celento. I agree.

DR. REED: Michael Reed. I agree.

DR. NYKANEN: Dave Nykanen. I concur.

DR. ROSENTHAL: Rosenthal, agree.

DR. HUDAK: Mark Hudak. I agree.

DR. CUNNINGHAM: Melody Cunningham. I concur.

CHAIRMAN TOWBIN: Thank you. Dr. LaRussa has left for the day, so he's not on this vote.

Then we come to the question that the FDA is recommending continuing ongoing surveillance; do we concur? Show of hands for people. Good. Dr. Cunningham, we'll go back this way now.

DR. CUNNINGHAM: Melody Cunningham. I concur.

DR. HUDAK: Mark Hudak. I agree.

DR. ROSENTHAL: Rosenthal. I agree.

DR. NYKANEN: Dave Nykanen. I agree.

DR. REED: Michael Reed. I concur.

MS. CELENTO: Amy Celento. I concur.

DR. DRACKER: Bob Dracker. I concur.

DR. BAKER: Susan Baker. I concur.

DR. WHITE: Michael White. I agree.

DR. MINK: Jon Mink. I concur.

DR. YANG: Lynda Yang. I agree.

DR. WIEFLING: Bridgette Wiefling. I concur.

CHAIRMAN TOWBIN: All right, good. I guess that will allow us to move along, and we can talk about Voluven. Thank you all very much.

This is Dr. Ravi Goud who is a Medical Officer in the Analytic Epidemiology Branch of the Division of Epidemiology at the FDA Center for Biologics Evaluation and Research. Dr. Goud attended medical school at Ohio State and completed his preventative medicine residency at Johns Hopkins. Prior to joining CBER in 2011, he led a variety of projects funded by USAID, the