AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

IN JOINT SESSION WITH THE

DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

Friday, December 15, 2006

8:00 a.m.

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PAPER MILL REPORTING
Email: atoigo1@verizon.net
(301) 495-5831

PARTICIPANTS

John Edwards, M.D., Acting Chair, AIDAC
Lt. Sohail Mosaddegh, RPh., Pharm.D.
Executive Secretary, AIDAC

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE
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Joan Hilton, Sc.D., M.P.H.
Margo Smith, M.D.
Gregory Townsend, M.D.
Bernard Wiedermann, M.D.
Annie Wong-Beringer, Pharm.D.

DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE
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Susan Heckbert, M.D., Ph.D.
Arthur A. Levin, M.P.H.
Louis A. Morris, Ph.D.
Robyn S. Shapiro, J.D.

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Dean Follmann, Ph.D.
Carol Koski, M.D.
James Leggett, Jr., M.D.
Michael Marco, M.P.H.
Carl Norden, M.D.
Michael Proschan, Ph.D.
Janine Smith, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH
SPEAKERS (NON-VOTING)

John G. Bartlett, M.D.
William Lee, M.D.
Joanne L. Rhoads, M.D., M.P.H.
Leonard Seeff, M.D.

PATICIPANTS (Continued)

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
PARTICIPANTS (NON-VOTING)

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Mark Avigan, M.D., M.H.S.
Edward Cox, M.D., M.P.H.
Gerald Dal Pan, M.D.
John Jenkins, M.D.
Rosemary Johann-Liang, M.D.
Janice Soreth, M.D.

C O N T E N T S

C O N T E N T S (Continued)

FDA Presentation

P R O C E E D I N G S

Call to Order

DR. EDWARDS: Welcome to the second day of this combined meeting of the Anti-Infective Advisory Committee and the Drug Safety and Risk Management Committees.

I would like to begin by asking you to please turn off your pagers and cell phones for the entire day. It is customary for us to, again, go through the introductions. I would like to start with Dr. Jenkins.

Introductions

DR. JENKINS: Good morning. I am John Jenkins. I am the Director of the Office of New Drugs in CDER at FDA.

DR. COX: Good morning. I am Ed Cox. I am the Acting Director for the Office of Antimicrobial Products, CDER, FDA.

DR. DAL PAN: Gerald Dal Pan, Director, Office of Surveillance and Epidemiology, FDA.

DR. JOHANN-LIANG: Rosemary Johann-Liang, Deputy Director, Division of Drug Risk Evaluation.

MR. LEVIN: Arthur Levin, Center for Medical Consumers and the Consumer Representative on the Drug Safety and Risk Management Advisory Committee.

DR. WIEDERMANN: Bud Wiedermann, Pediatric Infectious Diseases, Children's National Medical Center, Washington, D.C.

DR. SMITH: Margo Smith, Adult Infectious Diseases at the Washington Hospital Center here in Washington, D.C.

DR. KOSKI: Carol Lee Koski, neurologist. I am working with the Guillain Barre Foundation right now.

DR. NORDEN: Carl Norden, infectious disease, Camden, New Jersey, University of New Jersey School of Medicine.

MR. MARCO: Michael Marco, Center for AIDS Care and Treatment Programs, Department of Epidemiology, Columbia University School of Public Health.

DR. EDWARDS: Jack Edwards, Harbor UCLA Medical Center, Adult Infectious Diseases.

DR. FOLLMAN: I am Dean Follman, Head of the Biostatistics Branch at NIAID.

DR. GUTIERREZ: Kathleen Gutierrez, Pediatric Infectious Disease, Stanford University.

DR. BRADLEY: John Bradley, Children's Hospital, San Diego, Pediatric Infectious Diseases.

DR. LEGGETT: Jim Leggett, Adult Infectious Disease, Providence Portland Medical Center and Oregon Health and Sciences University.

DR. HILTON: Joan Hilton, Professor of Biostatistics, UCSF.

DR. PROSCHAN: Mike Proschan, statistician, NIAID.

DR. MORRIS: Lou Morris, President of Lou Morris and Associates.

DR. TOWNSEND: Greg Townsend, Adult Infectious Diseases at the University of Virginia.

DR. HECKBERT: Susan Heckbert, Professor of Epidemiology, University of Washington.

DR. WONG-BERINGER: Annie Wong-Beringer, infectious disease pharmacist, University of Southern California.

MS. SHAPIRO: Robin Shapiro, Professor and Director of the Center for the Study of Bioethics, Medical College of Wisconsin.

DR. EDWARDS: If we could come back to the people we missed.

DR. SORETH: Janice Soreth, Division Director for Anti-Infectives and Ophthalmology.

DR. AVIGAN: Mark Avigan, Director, Division of Drug Risk Evaluation.

DR. ALEXANDER: John Alexander, Medical Team Leader, Division of Anti-Infective and Ophthalmology Products.

DR. EDWARDS: Thank you very much. Lieutenant Mosaddegh will now read the Conflict of Interest Statement.

Conflict of Interest Statement

LT. MOSADDEGH: Thank you, Dr. Edwards. Good morning.

"The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda and

all financial interests reported by the Committee's participants, it has been determined that all interest in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest with the following exceptions.

"In accordance with 17 USC, Section 208(b)(3), full waivers have been granted to the following participants:

"Dr. John Bradley for an unrelated research grant for a competitor for which his employer receives less than $100,000 per year; also for his unrelated consulting for a competitor for which his employer receives less than $10,001 per year;

"Dr. John Edwards, Jr., for related consulting for a competitor for which he receives less than $10,001 per year;

"Dr. Lou Morris for current unrelated consulting for two competing firms for which he receives less than $10,000 per year per firm, also for his past unrelated consulting for a competing

firm for which he receives greater than $50,000 per year;

"Dr. Carl Norden has been granted full waivers under 18 USC, Section 208(b)(3) and 21 USC 355(n)(4) for stock ownership in a competitor firm valued between $25,000 and $50,000 and for his unrelated consulting for a competitor for which he receives less than $10,000 per year;

"Dr. Carol Koski has been granted a waiver under 21 USC 355(n)(4), an amendment of the Food and Drug Administration Modernization Act for ownership of stock in a competitor valued between $5,001 and $25,000. Because this stock interest falls below the de minimis exemption allowed under 5 CFR 2640.202(b)(2), a waiver under 18 USC 208 is not required;

"Lastly, Dr. John Bartlett has been granted a limited waiver under 18 USC 208(b)(3) which allows him to give a presentation but not a vote for his membership in unrelated advisory boards for four competing firms for which he receives less than $10,001 per year per firm, also

for his past unrelated speaking for a competitor for which he receives from $5,0001 and $10,000 per year.

"Waiver documents are available at the FDA's Dockets Web Page. Specific instructions as to how to access the web page are available outside today's meeting room at the FDA Information Table. In addition, copies of all the waivers can be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

"In the event that the discussion involves any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

"With respect to all other participants, we ask, in the interest of fairness, that they address any current or previous financial involvement with any firm whose products they may wish to comment upon."

DR. EDWARDS: Thank you.

We will turn the meeting now back to Mark Moyer who will introduce the speakers who will continue with the safety discussions.

Sponsor Presentation

DR. MOYER: Good morning. Yesterday, we heard a lot about one of our adverse-event special-interest hepatotoxicity and there were a lot of numbers that were provided in that regard. Before we turn to the other adverse-event special interests, in the interest of time, to help ensure that we are moving forward, I would just like to have one slide and that is one of our epidemiologist experts that would just come forward and just give a perspective of the summary of what we heard yesterday in order to help with that.

I will introduce Dr. Jerry Faich who will provide that for us.

DR. FAICH: Good morning. I think it is challenging to try to summarize all of the information you heard about toxicity but here is an effort to do it.

[Slide.]

What you heard was that spontaneous reports in the U.S. for severe or serious hepatotoxicity amounted to 54 cases reported in a context of 6 million prescriptions.

There are differing definitions and you heard them on both severity in relationship but, at most, there are 2 to 12 irreversible hepatic-failure cases in those 54.

It seems to me that the best risk estimate is derived from the two large epidemiologic studies that you heard described. I would just point out those two studies are closed-system studies that captured all exposures over the defined period of time and, in fact, the exposures were on the order of 850,000 exposures of which 264,000 were for Ketek and, within those same systems, then, with a good deal of assurance, if there was a serious hepatic injury, it would have been captured.

The other feature of those studies is that they were comparative. As you heard, then, that the best rates, it seems to me, in I-3 study for

acute liver failure was zero cases in the telithromycin Ketek group of 127,000 exposures.

In the PHARMetrics Study, there were five unconfounded hepatic injury cases. These would be hospitalized cases trying to align it with some of the DILI discussion in an exposure of 137,000 prescriptions.

Perhaps the most important thing to take away, at least in my mind from those well-done epidemiologic studies it that risk did not differ between Ketek and comparator drugs. So I thought that might help at least to indicate that there certainly is hepatotoxicity at the severe end. This is what the data, to my mind--the best data--look like.

Thank you.

DR. MOYER: To continue with that in perspective, our other adverse events of special interest include exacerbations of myasthenia gravis. We heard yesterday that this was first detected from the European spontaneous reports. Not only was this a rare event, but it was also a

rare condition. So it gives us some confidence that we are able to detect significant rare events through the pharmacovigilance activities with that.

We will also review the syncope and loss of consciousness and visual. Our first presentation will be an overview of the safety experience with Dr. Barbara Rullo, part of our Pharmacovigilance Group at Sanofi-Aventis. Then I will introduce Dr. Kardon after that.

Overview of Safety Experience

DR. RULLO: Good morning.

[Slide.]

As I indicated yesterday, I would now like to describe other safety events of interest, our experience with these since the product was approved in April 2004.

First, I will briefly describe our visual experience and then syncope, exacerbation of myasthenia gravis and then conclusions.

[Slide.]

What was our visual experience prior to U.S. approval.

[Slide.]

In 2003, we prepared a comprehensive review of all relevant visual data. This was submitted to the agency as an integrated overview of the visual events, or IOVE. Information in this report included data from receptor studies which showed minimal binding at the muscarinic 1 and 2 receptors. This was at 30 times the human concentration.

Preclinical studies showed no relevant visual findings. In our clinical program, during our Phase III studies, we found that about 1 percent of the patients reported a visual event, most typically blurred vision. For this reason, we went back and did two Phase I studies. You heard about this a little bit yesterday. These were done at supratherapeutic doses, 2400 milligrams.

We were trying to identify the mechanism for blurred vision. While we did not identify that mechanism, we did exclude severe etiologies including narrow-angle glaucoma and retinopathy.

[Slide.]

We also evaluated the postmarketing data that we had available. This included the specific postmarketing data as well as information from the German observational survey. We took the data that was in the narratives from our MedWatch form and entered it into a clinical-trial database and analyzed it as if were clinical-trial data.

Results were very comparable to what we had seen during our Phase III program, the most common event being blurred vision, a transient event and fully reversible. There were a few more cases of severe events. In particular, we had two reports of transient reversible visual loss but, for the most part, these severe events were severe events of blurred vision and there were no documented ophthalmologic examination changes that occurred in these patients.

We also did a comparative reporting-rate analysis at this time looking at events that would impact driving with other marketed products. We did a literature review looking at visual events associated with other marketed products.

What did this assessment show us?

[Slide.]

Again, the most common experience was blurred vision. The onset was 1 to 2 hours after the first or second dose in about 60 to 70 percent of the patients. The duration was 3 to 6 hours, more common in females and those under 40. About 40 percent of the patients reported some impact on activity and this was most commonly an impact on reading.

There were no motor-vehicle accidents, no consistent examination findings. The event was fully reversible and there were no sequelae.

I want to take a moment to just mention about this female preponderance. It is a little bit difficult to completely assess. When you look at IMS data, you see that there is a 3-to-2 ratio of female to male in terms of use of the product.

Also, when we looked at our clinical-trial data, we saw that, if you look at overall adverse-event reporting, females report more than males in a 2-to-1 ratio. The ratio here for these

visual events is 3-to-1 so it is a little difficult to interpret this female preponderance.

As a result of this information at the time of approval, our label included a precaution regarding blurred vision, difficulty focusing and a caution to patients regarding operating machinery or driving a vehicle if a visual event occurred.

[Slide.]

What happened in our post-approval setting. As you heard yesterday from Dr. Edelberg, we did a postmarketing visual-commitment study. In this study, again, we used a standardized questionnaire in order to better characterize the visual events and we had an intensive follow up of any event, particularly serious events.

An analysis was done after telithromycin had been on the U.S. market for a little more than 20 months. This was submitted to the agency in October of this year.

[Slide.]

What did these results show? Well, the results were very consistent with the results that

we had seen during our preapproval period. The nature and the severity of events were very comparable. The only real difference is that we had two motor-vehicle accidents whereas we didn't have any before. These are global results. These are not just from the U.S. market.

In terms of exam findings, there were a few patients that were able to have exams in close proximity to the event. These patient had a decrease in visual acuity. But, other than these two findings, there was no difference in our pre- and post-approval experience.

[Slide.]

In order to gain a better understanding of the mechanism of the blurred vision, we did a study in monkeys. This was a study using electroretinography. Specifically, we were looking for any severe mechanisms that would account for blurred vision, particularly retinal adaptive processes.

During the study, we found on changes in the monkeys in doses up to 500 milligrams per

kilogram given as a single dose. This is 13 times the human concentration.

[Slide.]

So, conclusions. The visual effects have been very studied through preclinical and Phase I studies and our postmarketing visual commitment study. We have a Phase I study that is going to start this month. This is another supratherapeutic study in volunteers.

Here we are looking at electroretinography and visual-evoked potentials. Dr. Kardon will speak a little bit more about what might possibly come from this study in terms of mechanism.

Our results are consistent after an exposure of 28 million, that is that the most common event is blurred vision. It is a transient blurred vision. It is infrequent. There are rare reports of more severe events. Again, these are transient and, while we don't know the mechanism, the effect is reversible and there are no permanent sequelae. Again, Dr. Kardon will address these more severe events in his presentation.

Our label at the time of approval appropriately described the risk. It appropriately described the driving precaution and there was no revision that was performed.

[Slide.]

Syncope; during our Phase I studies, five subjects developed syncope. In each of these five cases, the patients had received supratherapeutic doses and they had had preceding G.I. events. So the assessment was that these were vasovagal responses.

[Slide.]

During our Phase III program, syncope was a rare event and when it was observed, it was similar for comparator. Also rare in the postmarketing setting, when we did observe syncope, the effects were not related to any drug-induced malignant arrhythmia. So, at the time of approval, once again, syncope was not included in our label.

[Slide.]

In early 2004, we began to see a cluster of reports from Japan. Specifically, we saw six

reports in six months. Two of these were associated with motor-vehicle accidents. So, at this time, we did a qualitative review of our data and we saw that about a third to a half of the patients had a preceding G.I. event. So our assessment was that these were secondary vasovagal responses.

Because of the nature and the severity of the event and the potential risk to patients who are driving or operating a vehicle or operating machinery, we included this in our label, in our corporate label, in September of 2004.

[Slide.]

We also did a preclinical study in dogs using a postural-tilt test. We wanted to ensure that this was not a direct effect of the drug. We used comparators as well as a standard control and we found that telithromycin did not have a direct effect on orthostatic response. This does not exclude the possibility of a secondary vasovagal response.

[Slide.]

This is a spontaneous reporting rate over time. You can see the white line is Japan, yellow is France, the blue is the U.S. and the red global. For us, these results are very comparable to the situation we saw in the United States with hepatic reporting after the Annals article.

In November of 2004, the Japanese revised their label. Our sales representatives went out and advised physicians of this change. There was also a Dear Healthcare professional letter sent out at that time. It also started to get some national publicity and this include a t.v. broadcast on December 21st of 2004.

Within the ten days after December 21st, we received nine reports of syncope in Japan. Prior to this, there had been one or two reports in Japan. So we see this very large increase in the number of reports of that period of time, the end of 2004, the beginning of 2005. Prior to U.S. approval within the U.S. and globally are all very consistent with Japan as an outlier.

At this time, we decided to do another

qualitative analysis of our data. We reviewed it again. Again, the nature and the severity of the events had not changed from what we saw previously, namely that these events appeared to be secondary vasovagal responses. They were primarily preceded by G.I. events.

So, even though qualitatively there was no change, there was quantitatively a change although only in Japan.

[Slide.]

So, syncope was identified during our safety surveillance program and evaluated through a preclinical study. The reports of syncope are a heterogenous group, about a third to a half being secondary to a vasovagal phenomenon. For about a third of the other reports, they actually seem to be a symptom of another primary event such as anaphylaxis or seizures.

Our postmarketing labeling update describes the risk and it also includes a precaution about driving.

[Slide.]

What about exacerbation of myasthenia gravis? In vitro, there are no receptor studies to adequately assess the potential for exacerbation of myasthenia gravis because the specific neuromuscular mechanism for muscle weakness has not been identified. In our clinical program, we do not have any reports of exacerbation of myasthenia gravis.

Then, in the postmarketing setting, in 2002, we had four reports of exacerbation of myasthenia gravis. On February 4, we received our fifth report and, within a few days after AFSAPS, the French regulatory authority, received this, they contacted our French affiliate and discussed this with them. This was brought up to the global level and subsequently we reviewed the data from these few cases with our external experts.

There was a very short onset after administration of telithromycin to the onset of the symptoms within a matter of a few hours, in some cases, even 30 minutes. Additionally, there was a very rapid recovery upon discontinuation of

telithromycin.

So, because of the nature and the severity of the event and the evidence for the potential causality, exacerbation of myasthenia gravis was added to our label.

[Slide.]

So, in 2003, myasthenia gravis exacerbation was added. There was a Dear Healthcare Professional letter sent in Europe. At the time of approval in the United States, it was included in our label. The information was actually communicated to the Myasthenia Gravis Foundation of America in 2003 and it was included in their newsletter in September of 2003.

Since the risk for exacerbation of myasthenia gravis was identified and our label was revised, the reporting rate outside of the United States and globally had decreased. You can see the report rate prior to U.S. approval was 3.2 and it had decreased by more than half to 1.4.

However, based on reports coming from within the United States and expedited to the

agency, the FDA raised concerns that, despite our warning, telithromycin was still being used in a population at risk.

[Slide.]

Therefore, in June of this year, our label was strengthened. It was revised to describe the severity of the event and strengthened to provide a warning about the nature of the event so that it would be less likely to be used in this population at risk.

Also, at that time, a Dear Healthcare Professional Letter was sent. Once again, we notified the Myasthenia Gravis Foundation in order for them to include it on their websites.

[Slide.]

In conclusion, the risk of exacerbation of myasthenia gravis was detected very early in our post-approval European surveillance and it was updated following post-approval U.S. surveillance in patients at risk. There was a rapid onset. It is frequently severe and there is a rapid resolution upon discontinuation of telithromycin.

It was included in our original label at the time of approval in the United States but the warning was strengthened in June of this year and sharped with professional organizations.

[Slide.]

So, in summary, based on the last day and a half of our description of our safety experience, Sanofi-Aventis, with the same team in place since January of 2001 and with intensified pharmacovigilance initiatives in concert with outside experts and thought leaders, has continued to evaluate the safety of telithromycin on an ongoing basis.

As with all antibiotics, telithromycin is not without risk but we understand what these risks are and have taken steps to identify those risks preclinically, clinically, in Phase I studies, Phase III studies, in our postmarketing study and through pharmacoepidemiologic studies.

While the product is not without risk, these risks have been communicated to healthcare professionals and to patients in order that the

risks be appropriately managed. Therefore, we believe telithromycin has a favorable benefit-risk profile.

Thank you, Dr. Rullo.

DR. MOYER: Thank you. To help put in perspective two of those adverse-event special interests, I would like to introduce Dr. Randy Kardon. He is an associate professor at the University of Iowa. He is a neuro-ophthalmologist and he will provide his perspective on the visual events.

Expert Review: Visual

DR. KARDON: Thank you for the opportunity to give my expert opinion about these visual adverse events.

[Slide.]

I feel comfortable in this role. As a neuro-ophthalmologist, I have about 20 years experience in evaluating patients who have ill-defined visual systems or unknown causes of visual loss. These patients need a very careful history--it is often difficult just from a

referring physician's evaluation to know what is going on--an a very careful exam.

Many of these patients may have problems anywhere from the front of the eye, the cornea or the lens, or the accommodative apparatus of eye to problems in the retina, optic nerve or higher visual areas of the brain cortex. These are the types of patients I am used to seeing.

I also have experience in carefully evaluating these patients with the exam including electrophysiologic studies and some of my own external funding has to do with understanding how these tests can be used to evaluate these patients.

I also have had some experience in evaluating patients who have permanent visual loss from drug toxicity. Some of the ones that we see are ethambutol toxicity to the optic nerve with permanent visual loss--these are pretty tragic cases--hydroxy chloroquine, or Plaquenil, toxicity to the retina and, more recently, some patients that have ischemic optic neuropathies that are associated with Viagra use.

I have personally read the reports of the visual adverse events associated with telithromycin and I do feel there is an association in a small number of patients, about 1 percent. But I can tell you, after reading over 1,000 of these reports, it is still not clear exactly what the cause of these visual adverse events is.

[Slide.]

What do we know about the visual side effects? Usually, they are reported as symptoms of bilateral blurred visual or difficulty focusing. There have been a small number of cases of dimming of vision, or darkening of vision. I am going to get back to that in just a second. And there have been some cases of double vision.

Most characteristically, the onset of these symptoms occurs during the first one to three hours after the dose of telithromycin. They resolve after cessation of treatment. So I am not aware of any permanent case of visual loss associated with telithromycin's use. That is heartening to me.

Most patients that do have the visual systems are able to carry out their normal activities. But, in some severe cases, these patients can't drive or read. I think it is important that patients use their good judgement and not do things that require visual activity that then could compromise their safety or the safety of others. This is in the Package Insert.

I want to go back to the first bullet. My responsibility, in my mind, is to not only try to get my hands around what the cause of these visual symptoms are but to make sure there is nothing going on that is dangerous or that could cause permanent visual loss.

When I hear a patient that has dimming or darkening of vision, I worry about that symptom. That is the one symptom to a neuro-ophthalmologist that is worrisome. Blurring, or a little bit of difficulty of focusing, isn't that worrisome, to tell you the truth. So I want to talk just a little bit about that particular symptom and what it means to me.

[Slide.]

This dimming or darkening of vision; is it worrisome or dangerous? The reason why neuro-ophthalmologistx and ophthalmologists, why that gets their attention, is that the cases that we see in clinical practice, when a patient comes in with that symptom, is often due to vascular origin and they are often premonitory to vision-threatening, permanent visual-loss events.

They are worrisome because of that. Most of them are unilateral cases that are due to either retinal or optic-nerve blood-flow problems. There are bilateral cases of dimming or darkening of vision. Usually, these are hypotensive in origin affecting either the circulation transiently to the retina or optic nerve or the visual cortex at the occipital pole because this is a watershed area of the circulation. So drops in blood pressure can cause decrease in perfusion to that area of cortex and give this type of symptom.

But almost all those are accompanied by presyncopal fainting-like symptoms. That is what

is different about the handful of cases with dimming of vision from telithromycin. They are very rare. They are all reversible. They can last up to hours and they are bilateral and have not been associated with these presyncopal-like symptoms of hypotension.

[Slide.]

So what is causing these blurring and dimming visual symptoms? I think it would be easy to try to attribute this to some focusing problem on the accommodative muscles of the eye but I don't think that this really can explain all these events. The reason I have come to that conclusion is that, although many of them may be due to problems with focusing, the patients with blurring or focusing problem, that is their symptom, they don't have a shifted near-point or far-point of their vision.

That is what usually happens when you start to paralyze or excite the accommodative muscles. Also there is a lack of any evidence of muscarinic, adrenergic or acytlcholinesterase

effects of telithromycin and therapeutic doses. So that would argue against a direct effect on the ciliary smooth muscles in the eye that control focusing.

Finally, I have reviewed some reports of elderly patients with the side effects of blurred vision or lack of focusing. These patients have presbyopia, meaning they are old enough that they have to use bifocals anyway for near. They don't have much focusing range left. Some of them are pseudophakic, meaning they have had cataract surgery, they have got intraocular lenses and they don't have much ability to focus anyway. So it is hard to invoke an accommodative product to explain their symptoms in those patients.

[Slide.]

I think it is unlikely to be due to an effect of the drug on the cornea. There have been, really, no dry-eye or tear-film symptoms or findings on the reports at the time of onset and the duration is not compatible with this type of mechanism which usually takes longer to come on and

longer to go away. Also, the patients that have been examined by an eye-care specialist, there has been no sign of edema of the cornea or surface problems of the cornea.

[Slide.]

This leaves the following possibilities. The drug adverse effect may be interfering with the neuronal firing or conduction at either the retina or optic nerve or visual cortex. It is hard to separate those based on just reports.

A vascular effect, in my opinion, is less likely considering the bilaterality of the symptoms, the long duration of the symptoms, the reversibility, the lack of presyncopal symptoms and the predominance of this blurry symptom and the rarity of the dimming or darkening.

Although there is some evidence in the Phase I studies that there is a dose-dependent effect of the drug because, at very large doses of 2400 milligrams, some of these blurring effects were greater. There is probably an underlying susceptibility to the action of the drug at the

neuronal level and, perhaps, maybe there is some effect of a drug like this on mitochondrial activity--we know there is a gene heterogeneity of mitochondria in people and this is just a hypothesis--could affect mitochondrial function at either the retina or visual cortex transiently.

[Slide.]

So how might the FDA and industry approach this in the future. I have thought a lot about this. First of all, I can't emphasize more that we really need more detailed first-hand description of symptoms from affected patients either reported at a website or a telephone interview would be helpful. I can't stress that we need direct computer with the patient.

What I have learned in 20 years is that when a patient comes in with visual symptoms and you read their referring doctor's interpretation, they often go off the rails because they didn't listen carefully, they didn't know how to ask the patient about these symptoms. We really need more direct communication to get our hands around what

causes this.

I would like to see some type of guide for patients that they could look on what to expect maybe with some even visual examples and how to check their vision if symptoms should occur that could improve the quality of the symptom reporting in our interpretation.

Finally, I would like an opportunity to speak with, or that patients should have an opportunity to speak with or e-mail as the designated expert like myself that could be offered to a patient so I could have a more direct assessment of what exactly the patient was seeing when they had the symptoms.

In some cases, I think we should see if the patient is willing to have a rechallenge under a controlled environment. So we take the small number of patients that do have the symptom and try to rechallenge them and look for what is going on.

[Slide.]

So what do these reports mean to me as a visual expert? All the reports that you have heard

have been reversible to our knowledge. We conclude there is no known perceived permanent damage to the visual system. I think that is good.

The incidence of the adverse visual effects is rare. It is less than 1 percent. That tends to imply to me an underlying susceptibility in a minority of patients. The severe visual symptoms are even rarer. The patients need to be warned of this possibility and its potential impact on driving, operating heavy machinery, things that could be a safety concern.

Would I take telithromycin knowing these visual symptoms and reading all these reports? I would take this drug for the time period over which it is prescribed. I would discontinue the drug if I were one of the few patients that experienced the visual adverse effects I think mostly because, when a person gets visual symptoms, it creates a lot of anxiety. I think it is needless to re-expose them to the drug unless it is life-threatening if they don't take the drug.

I believe that the reports of transient

and reversible visual adverse effects are benign and would not prevent me from taking telithromycin if prescribed.

Thank you.

DR. MOYER: Thank you, Dr. Kardon. Our next presenter is a neurologist at the Duke University, Dr. Donald Sanders, who will present his perspective on the exacerbations of myasthenia gravis and a little bit about myasthenia gravis as a condition.

Expert Review: Myasthenia Gravis

DR. SANDERS: Thank you and good morning.

[Slide.]

I am Don Sanders. I am a professor of neurology at Duke University where I also direct the Myasthenia Gravis Clinic. I have been a member of the Medical Advisory Board of the Myasthenia Gravis Foundation for many years and served as its chair at one point in the past.

[Slide.]

What I want to do this morning is very briefly give you an overview of this rare disease

and then to give you my take on the reported effects of Ketek in patients with this disease and then, finally, to end up with some recommendations that I, as a clinician, would make regarding this issue.

[Slide.]

Myasthenia gravis is a rare autoimmune disease in which there is an immunologic attack on the neuromuscular junction which produces ineffective transmission of impulses from the motor nerves to the muscle which results in weakness.

[Slide.]

The estimated prevalence in the U.S. is about 50,000 to 60,000, about 5,000 new cases a year. About 1 in 5,000 patients in the U.S. have it. Since it is a hard disease to diagnose and the symptoms frequently go unrecognized, the, true prevalence is probably higher than these numbers would indicate.

[Slide.]

In most patients, the symptoms begin with blurred vision or frank double vision or drooping

of the eyelids. In most cases, the weakness then progresses to involve other muscles, particularly those of chewing, swallowing and talking. It can be mild or it can be severe and it can be life-threatening if the respiratory or oropharyngeal muscles of swallowing are affected in the patient.

[Slide.]

The most severe manifestation of the disease is what is referred to as myasthenic crisis. That is when there is acute worsening of respiratory or oropharyngeal muscle strength which requires ventilatory support.

Crisis usually has a definable precipitating event. In most cases, this is an infection, most commonly an upper-respiratory-tract infection. Medications can also induce worsening of myasthenia even to the extent of producing crisis in some patients.

Then various systemic diseases such as hyperthyroidism can occur in these patients and precipitate acute worsening to this extent.

[Slide.]

It has long been recognized that certain medications, particularly antibiotics, can produce worsening in patients with myasthenia. The aminoglycosides were recognized in this regard almost 50 years ago. Subsequently, there have been reports that macrolides, fluoroquinolones and other antibiotics can do the same thing.

There are a number of cardiovascular drugs that can do this as well. Even the corticosteroids, which are a mainstay in our treatment of myasthenia, are know to have the potential for initially worsening the weakness.

[Slide.]

I have reviewed the reports of the exacerbations induced or associated with taking Ketek. There have been 60 such reports worldwide and 29 in the United States. Given the numbers of exposures, this works out to, at least in the U.S., about five such reports per million exposures. There have been seven deaths associated with taking Ketek worldwide, three of which were in the U.S. I

am going to come back to these in a little bit more detail later.

[Slide.]

Evidence that the medication is responsible for these exacerbations is based primarily on the temporal relationship between taking the medicine and the worsening. Acute worsening is what has been reported within hours but then rapid resolution. In several patients, there have been more than one episode associated with taking the medication.

[Slide.]

In response to their vigilance procedures, the EMEA, in 2003, issued this public statement of a precaution regarding the use of Ketek in patients with myasthenia. They concluded that it was not recommended in myasthenia unless other therapeutic alternatives are not available. They recommended that myasthenic patients immediately seek medical attention if their symptoms worsen, that these patients should be carefully monitored and that, if these symptoms worsen, then adequate supportive

mechanisms should be undertaken and the medication should be discontinued.

These recommendations were subsequently incorporated into the Package Insert at the time of approval of Ketek in the U.S.

[Slide.]

I have looked at the seven reports of fatalities in patients with myasthenia who took Ketek prior to their death and concluded that, of these seven, two were possibly, or probably, Ketek-induced exacerbations. Two of these were unlikely related because of the time relationships between taking the medications and their worsening. One of them was clearly and anaphylactic reaction and one was due to the mesenteric thrombosis in a patient who had taken Ketek six months prior to death. One of these reports would be characterized as hearsay without adequate information to evaluate.

[Slide.]

So, in conclusion, I think it is clear that Ketek can produce, or induce, exacerbations in

patients with myasthenia including fatal crisis. This was recognized by the ex-U.S. postmarketing surveillance by the EMEA prior to FDA approval.

Incidently, I would just point out that, in the study 3014 that has been referenced, there were five myasthenic patients in those 25,000 subjects. Two of these received Ketek without exacerbation and, thus, this study, had it been accepted, would not have identified these exacerbations in patients with myasthenia.

[Slide.]

Because of the recognition prior to approval of Ketek in the U.S., that it can produce exacerbations in myasthenia, the Package Insert included a caution and recognition of these exacerbations has led to dissemination of the risk information as we have heard earlier.

These include a modified package insert, Dear Doctor letters, notification of the disease-specific organizations and physician education.

[Slide.]

My recommendations regarding the use of Ketek in patients with myasthenia is that, number one, it should not be used unless there is no other reasonable choice available. The exacerbation risk should be compared with that of alternative antibiotics, particularly the macrolides and the fluoroquinolones. Incidentally, none of these contain package-insert information regarding the caution except for a mild caution in the Package Insert for erythromycin despite the fact that I think it is well recognized that these drugs can also induce such exacerbations.

One also has to take into account the specific risk of the infection to the myasthenic patient. The infection, itself, is of much greater danger to these patients than in the general population because the infection may induce a crisis.

Finally, if Ketek were to be administered with myasthenia, particularly in a patient who has any respiratory or oropharyngeal weakness, that this should be done under controlled circumstances,

preferably in hospital.

Thank you.

DR. EDWARDS: Thank you, Dr. Sanders. We will now turn to the FDA for continued discussions on the visual and myasthenia toxicities. These will be led by Dr. Wassel.

FDA Presentation

Visual AE, Loss of Consciousness and Myasthenia Gravis Analyses of AERS Reports

DR. WASSEL: Good morning.

[Slide.]

My name is Ron Wassel. I am a safety evaluator in the Division of Drug Risk Evaluation in the Office of Surveillance and Epidemiology. Today, I will be discussing vision disorders, disturbances in consciousness and exacerbations of myasthenia gravis reported to the FDA with the use of telithromycin.

I will then conclude with points to consider for the manufacturer of these risks.

[Slide.]

As we have heard, vision disorders were a

known effect at the time of approval. They were seen in Phase III clinical trials and were subsequently a labeled event. We had conducted two reviews, a first review in March of 2005 as the drug approached its one-year approval anniversary and a second review in July of 2006 to assess the cases received from the end of the first review.

[Slide.]

During the pre-approval medical review, it was noted that these were the most commonly reported postmarketing events since approval in Europe and South America. Blurred vision, unspecified visual disturbance, accommodation disorder, diplopia and reduced visual acuity were the terms that accounted for 96 percent of the ex-U.S. visual adverse-event reports.

[Slide.]

This table is modified from Ketek's labeling and provides the incidence of all treatment-emergent visual adverse events in controlled Phase III studied by age and gender. The group with the highest incidence was females

under the age of 40 while males over the age of 40 had rates of visual adverse events similar to comparator-treated patients.

For each of the reviews, a broad search was conducted using a comprehensive set of terms to capture a wide array of visual events as different preferred terms may be used to report visual adverse events which are part of the same adverse-event syndrome.

It is very common for different patients to report similar visual symptoms in different ways. However, the limitation and searching over a wide group of visual adverse events is that it does not account for related pathology among the different events.

[Slide.]

Two searches were conducted, an initial search in which all cases of visual events were identified and a second search restricting it to for cases with a serious outcome per the FDA regulatory definition which includes cases of death, disability, hospitalization, those

considered to be life-threatening or required intervention to prevent impairment and/or damage.

At the time of the first review in 2005, which encompassed an 8-month period post-approval, vision disorders accounted for approximately one-quarter of all adverse-event reports for telithromycin submitted to the agency and a little less than half of these were considered serious.

Now, these figures represent crude counts which may include duplicate reports and have not undergone a medical/clinical assessment to exclude cases.

Therefore, at that time, we concluded that these events were consistent with those seen prior to approval in worldwide experience and as described in the then-current labeling which listed them under the precautions. Therefore, no recommendations were made for a labeling change.

[Slide.]

However, the continued receipt of a sizable number of reports prompted our concern to conduct a second review which was conducted in July

of this year. Again, the search terms were identical and the criteria used were the same as that done in the previous review.

[Slide.]

Over the 16-month review period, the agency received 276 reports of vision disorders which accounted for approximately one-fifth of all adverse-event reports for telithromycin over that time period. Approximately one-third of these were considered serious in nature. Again, these numbers are crude counts.

[Slide.]

Of the 276 cases, the most frequently reported events were blurred vision, visual disturbance and diplopia. Now, these numbers are not mutually exclusive as a single case may contain multiple adverse-event terms related to vision.

[Slide.]

The second search for serious cases retrieved 95 cases. These underwent a hands-on review from which 71 unique cases were obtained after excluding duplicate and those deemed

unrelated. The most frequently reported events were blurred vision and diplopia.

[Slide.]

The clinical characteristics of these 71 cases showed that the events primarily occurred in females. The median and mean age was around 40 years of age and the onset typically occurred on the first day of therapy within an hour or two of the dose although one case reported the onset one week after completing a five-day course of therapy.

[Slide.]

The outcomes of these serious cases included one case that was considered life-threatening as it occurred while the patient was driving which did not result in an accident. There were five hospitalizations and four emergency-room visits. 13 cases were considered disabling as the event impacted activities of daily living such as reading, watching television, driving, working, walking and riding.

One case described an intervention, the use of an eye patch for diplopia. 47 patients

eventually discontinued use of the drug. 53 cases reported resolution of the events and recovered. There have been no deaths or permanent disability related to vision disorders reported to date.

[Slide.]

The duration of effect is typically less than a day. Four cases reported lingering effects that range from five days to six weeks.

[Slide.]

An example of a case is presented here in which a 17-year-old female started Ketek, 400 milligrams daily, for sinusitis. She experienced blurred vision and diplopia about four hours after her dose. She also experienced difficulty or slowness in focusing.

The events would resolve after about 12 hours only to recur with subsequent doses. These events prevented the patient from engaging in normal activities of daily living and Ketek was eventually discontinued.

[Slide.]

So, in summary, for vision disorders,

there have been continued reporting of adverse visual events which include a sizeable number of reports, many with serious outcomes impacting activities of daily living. Blurred vision and diplopia are the most frequently reported events. There is typically a rapid onset and it has frequently led to discontinuation of the drug and occurs more often in females.

[Slide.]

Moving on to disturbances in consciousness. As was done with the review in vision disorders, two reviews were conducted in March of 2005 and, again, in July of 2006.

[Slide.]

At the time of the 2005 review, reports of loss of consciousness associated with the use of telithromycin that were submitted to the agency following approval generated concern within the agency. Also, the sponsor proposed, at the time, to add a statement under Nervous System in the Postmarketing Adverse Event Subsection of the Adverse Reaction Section noting rare reports of

syncope usually associated with vagal syndrome.

[Slide.]

In search for disturbances in consciousness, a broad net was used as there are many reasons people lose consciousness. The disturbances-in-consciousness group contains various terms pertaining to loss of consciousness which are listed here.

[Slide.]

Our search in 2005 showed that the reports that were submitted were almost all serious in nature. Again, this was defined as cases which resulted in a death or disability, was life-threatening or required hospitalization or investigation to prevent impairment or damage.

[Slide.]

Because of the high number of reports that could potentially lead to serious outcomes such as road-traffic accidents while driving, the agency recommended to also include wording in the Precautions Section of the label. The sponsor agreed to these changes and, subsequently, the

labeling was revised in October of 2005 to include statements related to syncope in both the Precautions and Adverse Reactions Section.

[Slide.]

A second review was conducted in July of 2006 with the same criteria as in the 2005 review. Again, we see that the reports that have been submitted are primarily serious in nature with approximately 85 percent of all disturbance-of-consciousness reports considered serious.

[Slide.]

The initial search found that there were various event terms reported with loss of consciousness being the most frequent. Again, these are not mutually exclusive.

[Slide.]

We then looked at the 72 cases with the serious outcomes after removing duplicates and excluding cases in which the disturbance in consciousness was part of a constellation of symptoms of a disease process such as sepsis,

hepatic failure, a seizure disorder. A total of 23 unique cases were obtained.

The focus was to identify cases that occurred in relatively otherwise healthy patients in which a disturbance in consciousness was unexpected and could be directly attributable to the drug.

[Slide.]

The clinical characteristics showed that the cases were almost equally divided between males and females and the median/mean age was around 46 years of age.

[Slide.]

The onset occurred over varying time periods but, typically, within the first day of therapy and most frequently within two hours of a dose.

[Slide.]

There were two cases that were considered life-threatening as they occurred while the patient was driving. In one case, no accident occurred. In the other case, an accident occurred in which a

pedestrian was killed and the patient was injured. One case resulted in a disability as the patient fell and sustained a vertebral compression.

[Slide.]

Examples of cases include a 62-year-old female who started Ketek 800 milligrams daily for bronchitis. ON Day 4 of therapy, while working, she experienced three syncopal episodes of sudden onset. An electrocardiogram was performed within five minutes revealing bradycardia with a rate in the 40s. She was hospitalized for observation and recovered.

[Slide.]

The second case involves an 18-year-old male who started Ketek 800 milligrams daily. The patient lost consciousness while driving to school, ran a red light, struck and killed a pedestrian. The patient also experienced a syncopal episode. All tests at the time were negative.

A follow-up from the patient's parents indicated that patient took his dose in the evening and the next morning passed out while driving. The

parents indicated that all medical evaluations have been normal with no abnormalities found.

[Slide.]

So, in summary, for disturbances of consciousness, the reports that we have received are primarily serious in nature. Two occurred while the patient was driving, one resulting in a fatality. There may be more than one etiology. It is not always clear that a vagal reaction has occurred. It is known that telithromycin has the potential to prolong at QT interval and, in fact, one case reported torsade de points.

[Slide.]

We do have cases of loss of consciousness in AERS that are poorly explained. At least one of the cases of loss of consciousness did occur in association with documented torsade. At this time, AERS does not have a strong signal for torsade. However, many of the cases lack sufficient data to reach a definitive conclusion on this and there are plans to monitor this further to see if it is possible to get more details on these cases that

may be torsade.

[Slide.]

Moving on to exacerbation of myasthenia gravis.

[Slide.]

Exacerbation of myasthenia gravis was identified through foreign postmarketing safety data and was a known event at the time of U.S. labeling, at the time of U.S. approval and was, therefore, a labeled event.

[Slide.]

The original labeling, at the time of approval, included in the Warnings Section a statement that telithromycin is not recommended with patients with myasthenia gravis. This was also included in the Information for Patients Subsection of the Precautions Section.

The Patient Package Insert only stated that there had been reports of worsening myasthenia gravis in patients with myasthenia gravis but did not state that the use is not recommended in these patients or advised patients to talk to their

doctors before starting therapy with telithromycin.

At the time of approval, it was not formally contraindicated in patients with myasthenia gravis.

[Slide.]

Despite the strong warnings about the use of telithromycin in patients with myasthenia gravis, cases including fatalities continue to be reported post-approval. In June of 2006, the Ketek labeling was revised to add a stronger recommendation about the exacerbation of myasthenia gravis including reports of death to the Warnings, Information for Patients Section and the Patient Package Insert.

[Slide.]

The statement pertaining to exacerbation of myasthenia gravis in the Warnings Section was made more prominent and the wording was also changed to, "telithromycin should not be used in patients with myasthenia gravis unless no other therapeutic alternatives are available." It also noted that reports have included death.

[Slide.]

This information was also conveyed in the Information for Patients Section and all of this italicized text indicates the new wording.

[Slide.]

The Patient Package Insert was also updated to indicate that patients with myasthenia gravis should talk to their doctor before taking Ketek.

[Slide.]

A review was undertaken in August of 2006 to further summarize the reports and to explore the possibility of contraindicating the use of telithromycin in patients with myasthenia gravis. Two searches were conducted, an initial search with terms pertaining to myasthenias and a second search for all post-approval telithromycin reports with an outcome of death to capture potential reports of a possible myasthenia-gravis related fatal outcome.

[Slide.]

The search terms included respiratory failure and respiratory arrest as surrogates to

capture reports of myasthenia-gravis exacerbation or crisis with a serious respiratory outcome that did not specifically mention myasthenia gravis.

[Slide.]

A total of 33 cases were identified with a median age of 59 years. There was a breakdown of 20 females and 11 males and these were mostly domestic cases. There were four fatalities and seven reports of a life-threatening event. There were 15 hospitalizations.

12 out of the 29 patients with a history of myasthenia, or approximately 40 percent, were intubated. 23 out of 33 cases, or approximately 70 percent, were symptomatic after the first dose and there was a rapid onset of symptoms with a median time to onset of 1-and-a-quarter hours.

[Slide.]

Examples of cases include a 53-year-old female who took her first dose of 800 milligrams in her physician's office. Approximately 40 minutes later, she began her myasthenia crisis and was intubated. She was hospitalized, treated and

recovered.

[Slide.]

A second case involves a 48-year-old male who took 800 milligrams of Ketek for sinusitis. In 45 minute to an hour and a half later, he experienced breathing difficulty and blurred vision. He had not taken Ketek in the past but was stated to be allergic to cephalosporin.

The patient was hospitalized with exacerbation of myasthenia gravis and respiratory failure and was on a ventilator for 13-and-a-half hours. The patient eventually recovered. It was also noted that the patient had been treated with azithromycin in the past with no reaction.

[Slide.]

In order to assess the reporting of myasthenia gravis exacerbation in association with clarithromycin in comparison to other antibiotics, a comparative review was undertaken in which telithromycin was compared to eight other similar oral antibiotics.

This review looked at domestic reports

based on the presence of an event listed under myasthenias or neuromuscular-junction dysfunction.

[Slide.]

This table shows a comparison of telithromycin with eight other antibiotics noting their date of U.S. approval. Although telithromycin is the most recently marketed of these selected antibiotics, it is currently associated with more cases of exacerbation of myasthenia gravis than all eight comparator agents combined.

Furthermore, six cases of telithromycin-associated myasthenia gravis resulted in intubation. Although a formal quantitative analysis has not been conducted, these data suggest exacerbation of myasthenia gravis may be more frequent with telithromycin than similar antibiotics.

[Slide.]

In summary, for myasthenia gravis, the severity of cases is reflected by the types of outcomes in the number of patients who required

intubation and in the rapid onset after a dose of telithromycin. The majority of patients experienced symptoms after the first dose.

[Slide.]

So, in summary, for these key safety issues, there is continued receipt of a sizeable number of reports of visual disorders impacting activities of daily living. There are serious reports of disturbances in consciousness including an automobile accident resulting in a fatality and there is continued reporting of serious cases of exacerbations of myasthenia gravis despite a labeled warning to only use when no alternative therapies are available.

[Slide.]

Later today one of the questions before you will be an assessment of the continued marketing of Ketek. If you should decide in the affirmative, the following are points for consideration for the management of these risks. For disturbances of consciousness, mechanistic studies should be conducted to elucidate the scope

of these effects in pathophysiology, whether anticholinergic, cardiac conduction or circulatory effects and, also, the change in the labeling from syncope to the more general disturbances in consciousness, as there are varying types of consciousness disorders not clearly explained by a single mechanism.

[Slide.]

For myasthenia gravis, the recommendation is to make the addition of the statement, "Telithromycin should not be used in patients with myasthenia gravis," to the Contraindications Section of the label.

[Slide.]

Overall, for these key safety issues, to develop a plan to inform and educate prescribers regarding these risks and to consider development of a medication guide to be provided to patients when the drug is dispensed.

Thank you.

DR. EDWARDS: Thank you very much, Dr. Wassel. We are now at the time for the committee

questions. I would like to remind the committee members to please try to catch Sohail's eye to get our cue for questions, if you will.

We will begin with Dr. Koski.

Committee Questions

DR. KOSKI: I have actually two questions and a comment. The first is the data that we were provided in our packet actually was for 5 million exposures in the United States. I know that there were additional exposures that were presented by the company.

In terms of the cases of myasthenia gravis, were there any additional cases that were identified with the almost now 6 million exposures in the United States of telithromycin?

DR. MOYER: Your question is if there are any additional events that have been reported for the exacerbation of myasthenia gravis.

DR. KOSKI: Yes.

DR. MOYER: I would ask Dr. Barbara Rullo. I think she had that in her presentation, actually.

DR. RULLO: Since we revised the label in June, there have been three additional reports of exacerbation of myasthenia gravis. In one case, the onset was clearly before the warning had been advised. In the other two cases, we don't have an onset date. We have been trying to follow up on it. So we have had three cases since. then.

DR. KOSKI: The next question is for Dr. Sanders. I wondered if you had any experience, yourself, in electrophysiology testing in any patients who might have had telithromycin.

DR. SANDERS: No; I have not. I have heard that three of my patients received Ketek from their family physicians without incident but I didn't have the opportunity to do any examinations following that.

DR. KOSKI: Thank you. Anyway, in expressing the rate of the effect of this drug on patients with myasthenia, it was at least expressed in our packet data that the incidence was 1.4 per million exposures. The point, actually, that I would like to make is that it really is a subgroup

analysis I think that would be more appropriate because it is patients who have damage to the neuromuscular junction, as Dr. Sanders actually very nicely expressed, that they do have a reduction in the number of acetylcholine receptors which is one of the reasons why they have recurrently weakness.

If you take the prevalence rates of, say, 14 per 100,000 in the population, within this group, there were probably close to 700 patients that were at risk for this.

If you look at that, it means that, basically, 1 in 25 patients were at risk for developing probably worsening of their myasthenia gravis. I certainly agree with the conclusion, or the recommendations, actually, that Dr. Sanders made that this is a drug that, if given to a patient with a known history of myasthenia gravis, should really only be done under controlled circumstances and not as, say, a prescription that is given and a patient going home and taking it in the community.

DR. EDWARDS: Thank you. Dr. Follman?

DR. FOLLMAN: Just to amplify on that, I agree. I thought the risk estimates for myasthenia gravis were looking at the population of all people instead of those who had myasthenia, 29 exacerbations out of 70,000 people in the U.S. who have it. A small fraction of those would be taking it. So the 1 in 25 seems a lot more plausible to me.

As Dr. Sanders pointed out, this is a rare disease. It is not an immune disease and there might be people who have it and don't realize it. That might be hard to give a number to but I was wondering if you would like to speculate on that.

A related question; getting at this idea of maybe there is a pool of people at high risk, the unknown myasthenics, were the exacerbations and the deaths in those who had more severe disease and, hence, would be more likely to be knowledgeable about it or were they in people who had less severe disease suggesting that it could happen to those who are not diagnosed.

DR. SANDERS: The risk of exacerbation and the seriousness of the exacerbation is directly related to the seriousness of the disease in the individual patient. Patients who have any respiratory symptoms from their myasthenia would be the ones most likely and most at risk for the crisis.

I guess the question is how likely is it that a patient with myasthenia who has significant respiratory involvement has not been diagnosed. I don't think that risk is very high.

On the other hand, I think any patient who develops any symptoms suggestive of myasthenia after taking Ketek or any medication should seek medical evaluation to see if they don't possibly have such an underlying condition.

Does that answer what you asked?

DR. FOLLMAN: I would also like the FDA, if they could comment on this idea of whether the exacerbations are largely in those who have the more severe form of myasthenia.

DR. AVIGAN: I think that we were not

really able to get that kind of detailed case information. I think what was most notable in the case material was the fact that when the myasthenia was expressing itself after treatment, the clinical outcomes were quite dramatic.

As you saw, there were a fair number of patients who were intubated out of the group. What they had at baseline and whether we could sort of segregate them into more severe and less severe was not possible.

DR. JOHANN-LIANG: I just want to add, though, there were a number of cases where it does appear that the patient was an outpatient patient pretty much healthy, eating dinner, has a history of ocular myasthenia only and then goes on to take a dose of Ketek and then has an issue.

Secondly, another point is that it is currently labeled to give only if there is no alternative therapy. However, again, the reports are not complete so that information is not available for the most part. But it is not clear to us at all whether this was taken as a treatment

of no alternative.

DR. EDWARDS: Dr. Smith.

DR. J. SMITH: A couple of questions related to the visual for the sponsor for Dr. Kardon and Dr. Rullo. The first question for Dr. Kardon; in light of the other presentations regarding the myasthenia and consciousness-related episodes and your recognition that accommodation may or may not play a role in this, especially in light of pseudophakic patients being included, is there any way that you can tie any of that information together in terms of us getting closer to designing mechanistic studies that would help us identify patients most at risk?

Clearly, if we could understand the mechanism behind that would help us to do that. I just wanted your perspective as a neuro-ophthalmologist putting that information together. Then I have a couple of other--

DR. KARDON: There are two parts to that answer. I believe the first part was--did you ask whether any of the myasthenic symptoms might be

related to visual symptoms.

DR. J. SMITH: Certainly they could be; yes. Just, in terms of mechanism, your speculation, certainly, regarding mechanism for the ocular visual complaints.

DR. KARDON: One study that is ongoing right now in normal subjects receiving a high dose of the drug is that multifocal electroretinography, a focal form of electrical response from the retina, and visually evoked potentials from cortex are being recorded to see if the visual symptoms can be precipitated at a high dose in normal subjects and to see if there is any electrophysiologic evidence, objective evidence, that that is going on.

So that might help shed some light. If you are asking me what other studies could possibly be done, there are two things, I think, that could be done. First, some type of functional imaging of visual cortex, either a functional MRI scan or optical imaging of cortical function in primates in your infrared that might show that the metabolic

activity of cortex is changed, is dose-related.

Secondly, there are some laboratories in the United States and around the world that isolated primate retinal preparations where the drug could be put on the top of the retina and the actual electrical response of the neurons and network of neurons, either in the outer or the inner retina, could be measured directly.

That is as high tech as you can get, probably, but those are two ways that are within reach to study such a question.

DR. J. SMITH: The proposed study with the normal volunteers, will there be a preponderance of women under the age of 40 since that is the group that has had the highest reporting rate?

DR. KARDON: I believe that is the way the study is being set up.

DR. J. SMITH: If there were to be additional studies such as fMRI, it could be included at that time to maximize the information that could be obtained from those subjects.

One other related question for Dr. Rullo

in her presentation and related to your comments, Dr. Kardon. The monkey study was a single dose albeit a 13-times human dosage and you did report ERG data--actually dark-adaptation data. Are there any other data available from that study?

DR. MOYER: The question is more of a preclinical toxicology question. That was performed by our preclinical. We can get someone to be able to address that for you. While they are coming to the area to be able to address that, there seemed to be a question regarding the myasthenia gravis still and the severity versus the occurrence. Dr. Rullo has information about that.

One of the other things is we already have updated the labeling. One of the evaluations we would need to see is has that been effective at decreasing the number of patients that have been treated with myasthenia gravis in an outcome. We really haven't had sufficient time to be able to evaluate that to see whether additional labeling would be required to prevent those cases.

DR. EDWARDS: Dr. Rullo.

DR. RULLO: Patients who were intubated were patients, for the most part, who had very severe respiratory infections. The patients with mild myasthenia had a mild reaction and recovered completely. There were about 10 to 15 percent of the patients where we saw an unmasking of the disease. About half of these patients actually reported that they had had some symptoms previously and they had gone undetected.

In discussions with Dr. Sanders, we understand that this is actually not atypical for a patient who has not been diagnosed previously to receive an antibiotic and then to manifest as myasthenia gravis.

DR. FOLLMAN: You mentioned that some of these patients were unmasked, I guess, because of this adverse event. Out of the 29 or so cases, how many were unmasked?

DR. RULLO: In the United States, there were seven cases that were unmasked. Four of these patients said that they had prior symptoms.

DR. MOYER: Back to the preclinical

question, I would like to introduce Dr. Doug Keller from our Preclinical and Drug Safety Evaluation Group at Sanofi-Aventis who can specifically address your question.

Could you repeat the question so we make sure we have it correct.

DR. J. SMITH: The question is related to the monkey study that was a single dose albeit a 13-times human dose. There was dark adaptation, reported normal dark adaptation. I wonder if there are any other data available regarding that study.

DR. KELLER: That study was solely focused on the electroretinography. We looked at both light adaptation and dark adaptation. There were no changes at all in either case. That is the only thing that was done in that study.

DR. J. SMITH: The other question is for the FDA for the comparators that were used for the visual symptoms. Can you identify which comparator antibiotics those were because the gender differences are not the same for the comparators. I think that is Slide 5 or 6.

DR. KELLER: I think you are talking about Slide 49 from the FDA presentation.

DR. J. SMITH: Slide 5, the comparators. There is not the female preponderance in the comparators. That is from the labeling? Okay, can somebody identify the comparators for this Slide 5 from the vision disorders where there is not necessarily a female preponderance there?

DR. JOHANN-LIANG: Those are clinical-trial data that is in the Adverse Events Section of the label. So the Ketek comparators in the clinical trials, I believe, were clarithromycin, Augmentin, cefuroxime, et cetera, so other oral antibiotic agents.

DR. J. SMITH: The reason I comment on that is there is quite a female preponderance in the Ketek-related visual reports. Clearly, as was stated by the sponsor, there is, in other adverse events, female preponderance of reporting a variety of adverse events. It that wasn't seen in the other antibiotics, does that help us to understand anything about the etiology and design future

studies in an appropriate way.

DR. JOHANN-LIANG: Gender differences with adverse events is an interesting topic. In spontaneous reporting, we do see that more females in general report adverse events across the board. However, that data really is from a controlled comparative setting. So the rate difference is really real.

We don't understand--there are mechanistic studies ongoing, but this was a point of discussion three months ago when we had the gemifloxacin advisory where there, again, young females had the highest frequency of cutaneous adverse reactions too. So this is a very interesting area and something that we have ongoing discussions about addressing gender differences of adverse events.

DR. AVIGAN: I would just like to add to that. I think that this is important because these are controlled studies and this is a synopsis of that development program. Clearly, there is a gender difference and that could be either--there are two possibilities in terms of categories.

There could be mechanistic differences in the gender and the other is the dose effect and effects based on weight and dose.

We did hear with visual disturbances that there is a potential that the higher drug-exposure might have a greater preponderance to this event.

DR. EDWARDS: Dr. Leggett.

DR. LEGGETT: I have sort of a silly question regarding visual events. If I were taking a drug and I suddenly couldn't see myself in the mirror, I would stop it. I would assume, in the controlled preapproval studies, when that happened, everybody stopped the drug.

I wonder, since the postmarketing, there are not instructions to stop the drug. It was noted by Dr. Wassel that 47, I believe, or some large number of folks, continued to take the medicine.

Did their symptoms worsen? Did they go away? What happened to those folks?

DR. ALEXANDER: For the preclinical information with regard to the controlled clinical

trials, we have to make a distinction between what we were seeing in terms of what are reported in postmarketing as much more severe reactions in terms of effects on vision.

So those people who have effects on their activities of daily living, "I couldn't see," are actually only data from either the foreign postmarketing that we had in the United States at the time of approval or from the U.S. postmarketing since that time.

What was seen within the controlled clinical trials was that patients reported mild blurring of their vision. If I recall correctly, it was only a proportion and I think it may have been a third, either one way or the other, that decided to stop the drug when they had these vision effects or that continued on.

One of the analyses that was done within the controlled clinical studies was to see was there a difference in terms of the resolution of these types of visual symptoms for those patients who continued the drug versus those who

discontinued.

Because what we had were just mild reports of patients who had some effect with the first dose and that most of them went away after that, a lot of the patients still continued to teak the medication without further visual problems.

So it doesn't give us the answer about what happens with those patients who are severe, we expect most of them do stop taking the drug when they have it.

DR. LEGGETT: What I was getting at--so it is not a dose-accumulation. It is more just sort of a concentration effect.

DR. ALEXANDER: Right. Again, 65 percent occurred with, like, the first or second dose and there is not really a lot of accumulation that is seen with this drug.

DR. WASSEL: I'm sorry if there was a misunderstanding. 47 patients discontinued telithromycin out of the 71 cases.

DR. MOYER: Is there still a question regarding the discontinuation of the clinical

trials because we do have that information if it is desired to have that presented. Does that still remain a question for someone?

DR. EDWARDS: Dr. Morris, you wanted to make a comment.

DR. MORRIS: Just a follow up. Is the same thing true for the loss of consciousness in terms of the time course of when that would occur. Is that also more likely to occur when someone initiates therapy and would they be okay or is an accumulation?

DR. ALEXANDER: I am not clear on that data. That is all from postmarketing.

DR. AVIGAN: I think Dr. Wassel did show us that there was a distribution of time to the event from initiation of therapy. There was actually some concentration in the first few hours suggesting some linkage to the dosaging.

Ron, do you want to just cover that again for us.

DR. MORRIS: I guess where I am going with this is we tell patients, be careful when you first

start taking the drug, be careful driving. I am wondering if, in this instance, would we be misinforming patients by saying that, in terms of the loss-of-consciousness issues in driving, they actually made it a more prolonged risk.

DR. AVIGAN: You have the data right there on that slide.

DR. WASSEL: Of the 17 cases where we had onset information, 12 out of the 17 occurred within the first day of therapy and seven of those within the first two hours of a dose.

DR. AVIGAN: The other important point about that is that these disturbances in consciousness etiologically may be heterogeneous. So we are still grappling with what is this mix of etiologies. Are some of these potentially cardiac arrhythmias? We don't know for sure. Are some of these vasovagal syncope events? They are probably a potpourri of different events.

DR. EDWARDS: Dr. Proschan?

DR. PROSCHAN: This is for Dr. Kardon. I am a little confused about what is causing these

eye problems. I thought that the briefing materials from sanofe-aventis said that the most likely cause was some kind of accommodation disorder whereas Dr. Kardon said that he didn't think that that was the cause.

Also I am wondering, he also talked about presyncope and thinking that that was unlikely to be the cause. I am wondering, in making that assessment, obviously, he is an eye person so he is looking at the eye events. But I am wondering if the syncope events have any relevance to whether the eye problems are related to that.

DR. KARDON: I think I can clear up that point. The original contention that the visual blurring may be related to the accommodative system is based on the Phase I study of a small number of normal subjects that were subjected to a high dose. In those subjects, none of them had any change in visual acuity measured at distance or near.

They had a very sensitive accommodomator that measures the dynamics of focusing, maybe too sensitive an instrument. There was some feeling,

although it wasn't a slam-dunk, that there were some changes in the dynamics of accommodation in normal subjects in a very high dose. So that is where that came from.

But you have to realize what has become apparent is that all of the postmarketing and controlled studies, those are all based on reporting of symptoms. Even the patients that were seen by an eye-care specialist at the time they have the symptom, which is very few, they had a completely normal exam.

So that is the dichotomy is that we don't have good information on the patients who are actually getting the event. The people that are taking the history that go into the reports, are usually not even ophthalmologists.

The second question, could you repeat that again?

DR. PROSCHAN: In making the assessment of whether these events were presyncope, you indicated that they weren't.

DR. KARDON: Ah, yes. Thank you. As a

neuro-ophthalmologist, we see a lot of visual problems not related to eye, too. So I am used to looking for things like that. In the visual adverse events that were more severe because their symptoms were more severe or they had the dimming or darkening, I specifically, when I was looking at those reports, was looking for any symptoms of dizziness or faintness or anything like that and have not been able to uncover any.

But I certainly was looking and interested, like you, whether some of those could have been related to a drop in blood pressure. Didn't get any feeling that that was the case.

DR. EDWARDS: Dr. Wiedermann.

DR. WIEDERMANN: This is also a disturbance-of-consciousness question. I got very different take-home messages from the sponsor and from the FDA. The sponsor seemed to say that these were likely mostly related to G.I. illnesses. I think the implication is these patients were so severely dehydrated, they had syncopal episodes. The FDA didn't really comment on that specifically,

I don't think. I would just like to hear some numbers of how many of these patients had severe vomiting and diarrhea. What are we talking about here?

DR. MOYER: So your question is regarding the syncope events and what patients had severe vomiting and nausea that might have led to dehydration.

DR. WIEDERMANN: Yes; more numbers than a general impression.

DR. MOYER: Dr. Barbara Rullo.

DR. RULLO: Slide on, please.

[Slide.]

We had a total of 154 reports of syncope. Unfortunately, about 50, 60, of these were not assessable because they just lacked adequate information. So there were 95 that we were able to evaluate. Of these, 32 had a preceding G.I. event and appeared to be vasovagal.

There were another third, approximately, that, as I mentioned, had some other--it was a symptom of another primary event, anaphylaxis,

seizures, myasthenia gravis. Then there were 26 cases for which there was an unknown mechanism and then seven cases which were considered cardiac in origin. These were people that had significant cardiovascular disease.

DR. WIEDERMANN: Thank you. But, of those 32 cases, how did you classify what counted as a G.I. event? I would think this would have to be severe G.I. illness to cause syncope.

DR. RULLO: Yes; there were patients that had significant vomiting and/or diarrhea. Some of the cases had some evidence of hypotension at the time.

DR. J. SMITH: I have a question regarding the current labeling for visual disturbance. I think a slide was actually going up a few minute ago.

DR. MOYER: Yes; actually, we were going to bring up that because the current package insert is in your briefing document from the sponsor as one of the appendices. I would like to ask Dr. Helen Edelberg who is most familiar with it because

she has been working on that extensively since the original labeling. Slide on. It is under our Precautions Section.

DR. EDELBERG: As you can see here, the visual-disturbance labeling did not change but it was descriptive in the Precautions Section, that it may cause visual disturbances particularly in slowing the ability to accommodate, an ability to release accommodation, and that these visual disturbances include blurred vision, difficulty focusing and diplopia. Most events were mild to moderate, However, severe cases have been reported.

Then it goes on with cautionary language. Patients should be cautioned about the potential effects of these visual disturbances--and syncope was added later--on driving a vehicle, operating machinery or engaging in other potentially hazardous activities.

If we turn to the next section of the label, I just wanted to point out something. In the Information for Patients, again you can see

that we indicate the same issues. We advise patients to avoid driving a motor vehicle, operating heavy machinery or engaging in otherwise hazardous activities if visual difficulties occur, also noting that some of these issues related to difficulties focusing, we provided advice on that and informed patients that they should contact their physicians if these visual difficulties interfere with their daily activities.

One more point that I wanted to mention with the next slide, 113, I believe.

[Slide.]

It was mentioned previously about the preponderance of females and people under 40. This is, indeed, captured in the labeling under the adverse-reactions section.

DR. J. SMITH: My question about the labeling as related to Dr. Kardon's comments and other comments related to whether accommodation is playing a role, clearly that is reflected there. But if there are other mechanisms for the visual disturbance not related to accommodation, having

only that in the label may lead a physician not to investigate other etiologies when they see a patient.

So I am concerned that the labeling doesn't reflect that. It does say the mechanism is unknown, absolutely. But if an ophthalmologist sees that, they may just assume, okay, it is accommodative and they may not do other studies that could help understand the mechanism.

It is not a question. It is just a comment.

DR. EDELBERG: I was just going to ask you if there was a question.

DR. J. SMITH: Just a comment.

DR. EDWARDS: Thank you. Dr. Hilton.

DR. HILTON: I just wanted to share with you a pattern that I have been noticing and that is that the sponsor has mentioned several times that the adverse events are similar to those seen with other antibiotics. But typically the dose for Ketek is 5 days exposure and the others are 10 days exposure.

Also, the multiple courses of Ketek are typically resulting in more severe or more adverse events such as in Dr. Lee's discussion yesterday of the very severe cases. Two of the cases were among those who took two courses of Ketek.

In Dr. Sanders' testimony, continued use of Ketek resulted in multiple episodes in the myasthenia-gravis patients. Dr. Kardon spoke about stopping treatment when the visual effects were noticed and possibly changing treatments. But other people have talked about prior exposure to antibiotics, shortening the latency and possibly being an additional risk factor.

Dr. Alex Walker's testimony yesterday talked about the sequential use of different antibiotics and how that may substantially raise the risk. So I don't think that stopping treatment and changing to another antibiotic appears to be a safe alternative. Just the duration of use of Ketek seems to be a strong risk factor for serious adverse events.

DR. EDWARDS: Thank you for those

comments. Would the sponsor like to respond at this time?

DR. MOYER: There were some comments regarding that. I think in particular your question or comment is about the sequence of the courses of telithromycin. Dr. Jerry Faich and I were discussing that this morning. I would say he has a perspective on that from those epidemiology studies which is what revealed that as a potential.

DR. FAICH: Just relative to hepatotoxicity, I entirely agree with you. I think that is one of the things that has signaled use in Alex Walker's I-3 data. So we were mindful of that as well and I think we were mindful of what we saw in the case series. We think that that definitely needs further analysis and is an area of concern.

So I would simply note that it demands more analysis actually and rather quickly.

DR. HECKBERT: Regarding that same data presented yesterday by Dr. Walker, I was looking at the handout that was passed out yesterday. He studied about 100,000 telithromycin users and about

100,000 clarithromycin users.

The handout says that there were 128,000 course of telithromycin and 132,000 courses of clarithromycin used in the period. Does that mean that somewhere between a quarter and a third of people are taking it at least twice?

DR. FAICH: Yes. That is exactly where we are going to go on this analysis. That is what we were discussing today. The same phenomena was there in PHARMetrics.

DR. HECKBERT: Yes. I was interested to see that. I was surprised to see that there appear to be so many people using it twice within a 60-day period or maybe back-to-back.

DR. FAICH: In PHARMetrics, it was over about 20 months. Here, I can't tell you what the general patterns are except that those patterns didn't vary between the two antibiotics. So I think your observation is right. It does provide us an opportunity--we looked at the five cases in PHARMetrics and they didn't have double exposure. So that is what I meant by we need to delve into