FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE NONPRESCRIPTION DRUGS ADVISORY COMMITTEE AND THE ARTHRITIS ADVISORY COMMITTEE

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Tuesday,
July 20, 1999

The Ballrooms
Holiday Inn Gaithersburg
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Gaithersburg, Maryland

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C O N T E N T S

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P R O C E E D I N G S (8:30 a.m.)

DR. BRASS: Good morning. I'm told this is working. I'm Eric Brass, chair of the Department of Medicine at Harbor-UCLA Medical Center, and chair of the Nonprescription Drugs Advisory Committee. I'd like to welcome everybody to this joint meeting of the Nonprescription Drugs Advisory Committee with the Arthritis Advisory Committee to discuss an NDA for 5-milligram Flexeril OTC.

We have a very large group, and so I would like to begin by going around the table and asking everybody to introduce themselves. That will also allow them to familiarize themselves with this high-tech microphone where you actually have to press the on button before you talk, and then please remember to press the off button because nobody else will be able to talk by pressing the on button.

So if we can start at the far end of the table, please, and if you can introduce yourself?

DR. HALDER: Rebat Halder, Department of Dermatology, Howard University.

DR. SHERRER: Yvonne Sherrer, rheumatologist, Fort Lauderdale, Florida.

DR. ANDERSON: Jennifer Anderson, statistician from Boston, Massachusetts.

DR. KRENZELOK: Ed Krenzelok, Pittsburgh Poison

Center and University of Pittsburgh.

DR. GERBER: Lynn Gerber, physiatrist-rheumatologist, Clinical Center, NIH.

DR. PUCINO: Frank Pucino, Pharmacy Department, Clinical Center, NIH.

DR. McNEELY: Carol McNeely, dermatologist, Washington, D.C.

DR. HARRIS: Nigel Harris, rheumatologist, Dean, Morehouse School of Medicine.

DR. BLEWITT: George Blewitt, industry liaison representative to the Nonprescription Drugs Advisory Committee.

DR. YOCUM: Dave Yocum, University of Arizona, rheumatologist.

DR. SACHS: Hari Sachs, pediatrics, Rockville, Maryland.

DR. TITUS: Sandy Titus, the administrator for Nonprescription Drugs Advisory Committee.

DR. NEILL: Richard Neill, family physician at the University of Pennsylvania.

MS. MALONE: Leona Malone, consumer rep for the Arthritis Committee, West Palm Beach.

MS. HAMILTON: Kathleen Hamilton, consumer rep to the Nonprescription Drugs Advisory Committee, and director of the California Department of Consumer Affairs.

DR. ELASHOFF: Janet Elashoff, biostatistics, Cedar-Sinai and UCLA.

DR. GILLIAM: Eddie Gilliam, family nurse practitioner, Tucson, Arizona.

DR. LOVELL: Dan Lovell, pediatric rheumatologist, University of Cincinnati.

DR. HYDE: John Hyde, Acting Deputy, Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, FDA.

DR. MIDTHUN: Karen Midthun, Acting Division Director, Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, FDA.

DR. KATZ: Linda Katz, Deputy Director, Division of Over-the-Counter Drug Products.

DR. GANLEY: Charlie Ganley, Director, Division of Over-the-Counter Drug Products, FDA.

DR. DeLAP: Robert DeLap, Director, Office of Drug Evaluation V, FDA.

DR. BRASS: Thank you all.

I'll now ask Dr. Titus to read the conflict of interest statement.

DR. TITUS: The following announcement addresses conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for a conflict of interest at this meeting, with the following exceptions. In accordance with 18 U.S.C. 208(b), full waivers have been granted to Dr. Mary Anne Koda-Kimble and Dr. David Yocum. A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information office, Room 12A-30, in the Parklawn Building.

In addition, we would like to disclose for the record that Dr. Steven Abramson has an interest in Merck. Dr. Kenneth Brandt has an interest in Merck, and Johnson & Johnson, the parent company of Ortho-McNeil. Dr. David Yocum's employer, the University of Arizona, has interests in Novartis. These unrelated interests do not constitute a financial interest in the particular matter within the meaning of 18 U.S.C. 208. Notwithstanding these interests, it has been determined that it is in the agency's best interest to have Dr. Abramson, Dr. Brandt, and Dr. Yocum participate fully in all matters concerning Flexeril.

In the event that the discussions involve 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. BRASS: Thank you.

I'll ask Dr. Hyde now to make some opening remarks.

DR. HYDE: Good morning and welcome to the members of the Nonprescription Drugs and the Arthritis Advisory Committees, the representatives of Merck, and to the audience.

The purpose of today's meeting is to seek advisory committee input on the application to market the muscle relaxant Flexeril over the counter. Flexeril is an approved prescription product, but currently there is no muscle relaxant approved for OTC use. Thus, this application under consideration represents an introduction of a new class of agents into the OTC market.

As Dr. Witter will describe shortly, the topic of muscle relaxants for over-the-counter use has been the focus of a process extending back over a decade. The

activities involved previous advisory committee meetings, several FDA divisions, including the Neuropharmacologic Drug Products, Analgesic and Inflammatory Division, OTC Division, as well as drug companies and members of the public.

A great deal of effort has gone into defining the questions raised by OTC muscle relaxant use and to trying to determine ways in which those questions might best be answered. Today's meeting is a major milestone in that process. Previous public meetings have been general or rather theoretical. Today we have a specific application before us. Today we have actual study results to consider. This promises to be a rich advisory committee experience, so in the interest of getting into today's business, I'll yield to the first speaker.

DR. BRASS: Thank you, Dr. Hyde.

Just a word about the format this morning. We will begin with the presentations from the FDA, followed by the presentations by sponsor. Because of the likelihood of many issues being addressed by both sets of presentations, I'm going to ask the committee to hold all questions for the FDA until after the sponsor's presentation, with the only exceptions being very brief questions of clarification. Otherwise, we will probably be here through tomorrow's meeting discussing this.

So, with that background, I'd like to ask Dr. Witter from the FDA to begin the FDA's presentations.

DR. WITTER: Can you hear me okay? Yes.

Good morning and welcome to today's combined meeting of the Nonprescription Drugs Advisory Committee and Arthritis Advisory Committee to consider Flexeril for over-the-counter use. This should be an interesting discussion, so please do as our friend is doing here and pay close attention.

Next slide.

Besides myself discussing briefly some of the background and efficacy with Flexeril, the other speakers today will be Dr. Lee discussing PK issues, Dr. Paul Andreason discussing the neurologic impact of Flexeril, Dr. Michael Klein discussing the abuse potential, Dr. Rosemarie Neuner discussing safety aspects, and Dr. Kathryn Aikin discussing label comprehension. I know that our speakers are excited and ready to go, so I'll try and move along here.

Next slide.

As Dr. Hyde has indicated, we have been discussing muscle relaxants in general or consideration for their use over-the-counter for a while now. This slide attempts to kind of get you some sense of history here. As you can see, I've broken this up into two groups, one

discussing muscle relaxants as a group of drugs and the other as single agents. The first meeting that I'm aware of was in 1982 when these compounds were in a different division. There were two subsequent meetings, the most recent being in March of 1995, which was also a combined meeting, as is today.

As single agents, there was a meeting in February of 1997 to discuss whether Soma should be a scheduled compound, and then, of course, we have today's meeting, which is the first to consider use of muscle relaxants over-the-counter in the U.S.

Next slide.

Now, in terms of what's gone on previously, there's been a lot of interesting discussion, as I'm sure there will be today, and I'd like to just present that for a bit here. In March of 1995, the following five questions were posed to the advisory committee meeting. I think it's fair to say that we didn't get much beyond the first question, which is: "Should muscle relaxants be considered for over-the-counter use?" I think part of the problem was trying to decide things in the absence of data, which is not the problem today.

Next slide.

Some of the discussion at these prior meetings involved the realization, for example, that muscle

relaxants are a diverse group of compounds, ranging from compounds such as Parafon Forte to Robaxin to Soma, and, of course, Flexeril. It was also appreciated that because most of these are old compounds, they were actually DESI'd into use because of the Kefauver-Harris amendment in 1962. But that was not the case with Flexeril. Flexeril, as we know, was submitted in December of 1975 and was approved in August of 1997.

Next slide.

The muscle relaxants, other issues were whether there was efficacy, and probably the best way to summarize both the DESI review and the 1994 clinical practice guidelines, which I believe is in your package, is that muscle relaxants as a group are probably more effective than placebo but not NSAIDs, and that contributes to why the labeling says "as an adjunct to" things like rest and physical therapy for the prescription muscle relaxants.

The mechanism of action was discussed and it was generally appreciated that these were not direct peripheral muscle relaxants, and there was a question as to whether, in fact, efficacy was because of their sedative properties.

Next slide.

The other discussion focused on who the target population is and is there a societal benefit for muscle

relaxants, especially over-the-counter? What is the frequency of spasm and pain in areas such as the back, legs, shoulders and neck? What is the nature of the prescribed use of muscle relaxants? Is the condition of back pain from muscle spasm self-recognizable? There was a lot of discussion about that issue, and I think we'll be discussing that again today. And would delay in diagnosis lead to serious consequences?

Next.

As I mentioned, these are, for the most part, old drugs, and there was also a concern that there's a large PK/PD knowledge gap as assessed by current standards. There was also discussion as to whether the prescription doses were too unsafe for OTC use, and if that was the case, then effectiveness and safety of the OTC dose must be established as we're discussing today.

There were discussions about whether general guidelines were possible, and, in fact, I'll describe something that was issued in 1986, but it was pretty much decided that each drug would really have to stand on its own merits.

Next.

Also at this meeting was described the proposed World Health Organization core set of outcome criteria for lower back pain, which included such endpoints as patient

global, time to and duration of improvement, forward flexion, quality of life index, disability index, and medication use.

Next slide.

Now, what I had mentioned as a letter in 1986 from the agency described some of the types of studies that should be considered for muscle relaxants over-the-counter. These were, for example, cognitive impairment and/or sedation in the elderly, usage trials to mimic over-the-counter conditions, PK trials in healthy volunteers, the elderly, with renal impairment, and cirrhotic patients, and then other types of trials to assess, for example, abuse potential, market/mall studies, et cetera.

Next.

So hopefully that sets some kind of a perspective on why we have the kinds of studies that we have today for Flexeril. There were in fact 13 studies submitted for this NDA. Four protocols dealt with clinical pharmacology PK, six protocols discussed psychomotor aspects, and three protocols were designated as Phase III clinical studies. Those were broken up into two types. There were placebo-controlled, which is Study 6 and 8, and there was a use trial, which was Study 9, which was an open-label study.

Next.

Just in the interest of time, I'll just briefly describe some of the results of these Phase III trials. In terms of looking at the patients in Studies 6 and 8 -- by the way, these were basically one-week studies -- there were, as you can see here, four groups, Flex 2.5, Flex 5, Flex 10, and placebo. The reason that there are more in the Flex 5 group, for example, is that this was a common dose between the two Studies 6 and 8.

The patients in Studies 6 and 8 had a physician rated moderate or moderately severe painful muscle spasm of the lumbar and/or cervical spine region. The spasm was at either less than or equal to 7 or 14 days, depending on the study, as is in front of you; whereas in Study 9, patients had self-diagnosed back pain.

Next.

Concomitant therapies. In Studies 6 and 8, analgesics, psychomotor agents, and muscle relaxants were not allowed. Yet there were a few patients in Study 6 who took NSAIDs in the Flex 5 group, and the four patients in Study 6 took aspirin. Just so we're on the same page, Flex 5 refers to 5 milligrams three times a day. Study 9, on the other hand, did allow analgesics, and, in fact, 16 percent of the patients took ibuprofen, and 11 percent of patients took acetaminophen during this study. Heat therapy was allowed, and anywhere from 27 to 38 percent of

patients used this modality.

Next.

In terms of looking at Studies 6 and 8, overall the completion rate was 86 to 93 percent. The discontinuations were really primarily for two reasons, either clinical adverse events or ineffective therapy. As you can see here, for example, in Study 6, Flexeril 10 was significantly different than placebo in terms of withdrawal for clinical adverse events, whereas for ineffective therapy, the Flex 2.5 in Study 8 was different than Flex 5. This generally depicts, although I'm not showing all the data today, the tendency that at the higher doses of Flex 5 and Flex 10, patients tended to withdraw because of clinical adverse events, whereas with Flex 2.5 and placebo they tended to withdraw from the trials because the therapy was ineffective.

Next slide.

Primary endpoints in Studies 6 and 8 in the placebo-controlled trials were basically all patient-derived 5-point categorical scales. For example, a global impression of change, medication helpfulness, and the diary card, relief from starting backache. The global impression was also the variables studied in Study 9.

Next slide.

Again, in the interest of time, I'm just going

to show some of the results here. This is patient global at Visit 3, which is essentially at the one-week time point. The results are consistent, so this is really representative. You can see here is depicted the mean and standard deviations in both Studies 6 and 8. As you can see, Flexeril 5 and Flexeril 10 in Study 6 were significantly different than placebo, although the effect sizes appear modest. In Study 8, Flexeril 5 again does distinguish itself statistically from placebo, whereas Flex 2.5 does not. Again, the results appear to be clinically modest.

Next slide.

Now, I'm not describing the other primary endpoints of medication helpfulness and the diary. They were, again, basically the same type of results. I'd just like to describe briefly the secondary results of physician rating of muscle spasm. This was again on a 5-point categorical scale ranging from zero/none to 4/severe board-like muscles.

Next slide.

Looking at the results for this secondary variable, again at Visit 3, here I've depicted the mean change from baseline, and as you can see, in Study 6, Flexeril 5 and Flex 10 again do separate from placebo, but again the results appear to be clinically modest, and the

same applies for Study 8 in that Flex 5 does separate from placebo but Flex 2.5 does not.

Next slide.

Now, in terms of discussing and thinking about whether Flexeril works, one could argue that it is useful to focus on the distinction between efficacy and effectiveness. It is widely accepted that in a randomized clinical trial, like Studies 6 and 8, efficacy means that the treatment produces a reduction in the probability of experiencing the adverse outcome in the study group being investigated. Efficacy, however, needs to be distinguished from effectiveness. Effectiveness implies that the treatment works under usual conditions of use as opposed to conditions of investigation. It is possible to perform trials to assess effectiveness.

So it could be argued, for example, that efficacy and the question of whether efficacy was established in Studies 6 and 8, the problem is that, for example, there were not a lot of elderly patients, and so efficacy cannot be necessarily true in all the subgroups. Effectiveness in Study 9 was probably not demonstrated for several reasons, because of a lack of a control group, either active or especially a placebo-control group, because of lack of physician verification of the muscle spasm as the cause of the pain, because of the use of

concomitant analgesics and NSAIDs which confounded the results in the trial, and really because also of a lack of endpoints. In this case you'll recall that there was only a patient global being studied in Study 9.

Next slide.

So some of the issues that we will probably be discussing today are: Has, in fact, the effectiveness for OTC use been established? This will probably come down to a discussion of statistically significant results but are they clinically meaningful? I'm sure there will be a discussion again as to whether back spasm as a source of back pain is, in fact, self-recognizable, and were the appropriate endpoints studied?

Thank you.

DR. BRASS: Any clarification questions for Dr. Witter?

(No response.)

DR. BRASS: Do you want to go ahead and just introduce your next speaker?

DR. WITTER: Our next speaker is Dr. Lee.

DR. LEE: Good morning. My name is Sue-Chih Lee. I'm the pharmacokinetics reviewer for the Flexeril NDA. I will talk about pharmacokinetic issues of this drug.

Next, please.

To support this NDA, the sponsor conducted four pharmacokinetic studies, one study to determine single and multiple dose pharmacokinetics and dose proportionality, one study in elderly subjects, and one in hepatic impairment patients. A study to determine bioavailability/bioequivalence was conducted to determine the performance of a new formulation, also provided literature articles and study reports. Of those, the ones related to drug metabolism and drug-drug interactions are considered most relevant.

Next, please.

I will go through briefly the pharmacokinetic characteristics of cyclobenzaprine and then talk about issues. First, absorption and bioavailability. After a single dose administration, peak plasma concentrations occurred at four to five hours after dose. The absolute bioavailability is about 0.55.

Next, please.

This slide shows the plasma concentration time profiles. The left-hand side shows profiles after a single dose administration, and the right-hand side is for after multiple dose administration. Three doses were studied, 2.5 milligrams, 5 milligrams, and 10 milligrams. As you know, the prescription dose was 10 milligrams TID, while the proposed OTC use is 5 milligrams TID. Those

proportionalities were established for the three doses studied. It's apparent that plasma concentrations increased substantially after multiple dose, as you can see from here. This is after multiple dose, and this is after single dose. The accumulation ratio is about four-fold.

Next, please.

Plasma protein binding, based on a literature article, is about 93 percent for cyclobenzaprine, over a concentration range of 0.1 to 1 microgram per mil. We do not have information on binding in the therapeutic concentration range, which is close to 0.01 micrograms per mil. However, it's expected that protein binding will be 93 percent or greater than the therapeutic concentration range, depending on whether the binding is linear or non-linear.

Next, please.

Elimination of cyclobenzaprine is primarily through metabolism, while biliary excretion and renal excretion played only minor role or even negligible role. The effective half-life of cyclobenzaprine is about 18 hours in healthy young subjects.

Next, please.

This slide shows the proposed metabolic pathway for cyclobenzaprine. As you can see, several metabolites were found. Glucuronide to N-demethylated products were

considered the major metabolites. However, this scheme may not represent the total picture, as the reflection of the dose was not accounted for.

The sponsor conducted in vitro studies to identify what cytochrome P450 enzymes were responsible for the metabolism of cyclobenzaprine. The individual studies show that N-demethylation reaction was mediated primarily through CYP 3A4 and 1A2, while CYP 2D6 played a minor role. The sponsor concluded that genetic polymorphism is not a major concern because CYP 2D6 plays only a minor role, and also there is a low potential for inhibition of cyclobenzaprine metabolism by other concurrent medications due to multiple metabolic pathways and cytochrome P450 involved. However, we do not consider the study as definitive because the studies were conducted at a much higher cyclobenzaprine concentrations than the therapeutic levels.

Next, please.

I will talk about pharmacokinetics in special populations, including elderly and hepatic impairment patients. First, a study was conducted in elderly subjects. Historical data in young subjects were used as comparison. In elderly subjects, longer effective half-life was found, which was about 33 hours as compared to 18 hours in young volunteers. The AUC in elderly was 85 to 95

percent higher than in young subjects. Steady-state concentrations in elderly subjects after 5 milligram TID dosing was similar to that observed in young volunteers after 10 milligram TID dosing. Because of this elevated plasma concentration in elderly patients, we consider that dose adjustment should be considered for elderly patients.

Next, please.

This is just to illustrate the plasma concentrations at steady state. This is for healthy elderly, while this is for healthy young subjects. When I say healthy, it just means that there is no, say, liver disease or heart disease. As you can see, the plasma concentration in the elderly is about twice as high as in the young subjects.

Next, please.

This is about hepatic impairment patients. The study was conducted in 16 mild to moderate hepatic impairment patients, and also there were 8 healthy control subjects who were age matched. However, we found out that there was only one patient that had moderate hepatic impairment based on the Child-Pugh classification. Therefore, we consider this basically a study in mild hepatic impairment patients.

Next, please.

Again, the effective half-life in hepatic

impairment patients were found to be higher than in control subjects, resulting in elevated plasma concentrations. It was also observed that many patients had not reached steady state at the end of the study, and therefore plasma concentration and a degree of accumulation will be even higher than what was observed in this study.

Next, please.

This is just to show again the plasma concentrations. The upper curve is for the hepatic patients, and the lower curve for healthy controls. This is just to show that the concentration in hepatic patients are elevated.

Next, please.

I will go to PK considerations in OTC switch. First of all, for special populations, as I have mentioned, in elderly and mild hepatic impairment patients, there were elevated plasma concentrations, and we would recommend dosage adjustment in these patients. For moderate or severe hepatic impairment patients, there are no information in these patients, and therefore we consider cyclobenzaprine should not be used in these patients.

Another consideration is for pediatric population. There is no PK studies, and therefore we consider it necessary for the sponsor to conduct studies in pediatrics so that dosage determination will be based on

scientific data. Of course, these are for the committee to consider.

Next, please.

Another consideration in OTC switch is drug-drug interactions. There are pharmacokinetic interactions with several drugs which are already in the label, and I will mainly focus on the pharmacokinetic interactions. Although there are no clear signals from the prescription products about drug-drug interaction potentials, however, based on the data we have, we cannot rule out the potential at this time.

The sponsor did conduct studies to determine whether the metabolism of cyclobenzaprine can be inhibited by other concomitant medications. However, as I mentioned before, the study to identify primary cytochrome P450 enzymes was not definitive, and further research is needed. Another aspect is whether cyclobenzaprine can act as an inhibitor of the cytochrome P450 enzymes and therefore inhibit the metabolism of other concomitant drugs. An in vitro study was conducted for this purpose. However, the study did not include cytochrome P450 2C19 substrate, and the study in 2D6 was high 2D6 substrate concentrations. Therefore, we considered in vitro study with these two isozyme substrates are necessary. Again, these are for the committee to consider.

Next, please.

With slowly evolving information, another implication is about the prescription label. The prescription product was approved in 1977, and there was limited pharmacokinetic information. With the new information that we have, we think that the future work should also include revision of the prescription label and mostly with the information related to drug metabolism and information in special populations, and possibly also dosage adjustment.

Thank you. This concludes my presentation.

DR. BRASS: Dr. Yocum?

DR. YOCUM: With the effects in the P450 system, does grapefruit juice affect metabolism at all, or is that known?

DR. LEE: I do not know, especially at this point. I don't know exactly what is the cytochrome P450 responsible for the metabolism of cyclobenzaprine.

DR. BRASS: Thank you.

We're going to shift order again and ask Dr. Klein to discuss the abuse potential.

DR. KLEIN: Good morning. With this NDA the sponsor had submitted data related to drug abuse and drug misuse of the product. The sort of data that was submitted is what we usually use within our division for a review of

drugs for scheduling under the Controlled Substances Act. This is largely epidemiological data. It's data that's related to usage problems, to problems that occur with actual use of the drug. We never use it as stand-alone. We use it to complement pharmacological data, the way that a drug is used in treatment, as well as interactions of the drug with other likely concomitant medications.

Could I have the next slide, please?

The three data systems which were addressed in the sponsor's NDA were data from the Drug Abuse Warning Network, or DAWN, Poison Control Center reports from the American Association of Poison Control Center's Toxic Exposure Surveillance System, and adverse events reports. In addition to review of the sponsor's submissions, we independently went into the separate databases and looked at the information ourselves.

Could I have the next slide, please?

Briefly, DAWN identifies substances that are associated with drug-induced or drug-related emergency department visits, and medical examiner or coroner deaths. It's used to track increases or decreases in abuse or misuse of a drug. The emergency department data on the next slide, please, is from a selected sample of approximately 500 hospital emergency departments in 21 major metropolitan areas across the United States, and it's

used to product estimates of drug abuse visits to emergency departments in the U.S. The medical examiners data comes from approximately 175 jurisdictions and collects information on drug-related and drug-induced deaths involving both legal and illegal substances. Death has to be directly caused by the drugs, such as a fatal overdose or possibly an accident or a homicide that's related to drug use in order for it to enter into the system.

Next slide.

Now, the emergency department visits are included in DAWN if the drug is illegal or legal and used inappropriately or displays evidence of dependence or is used intentionally for psychic effects or for suicide attempts. Accidental ingestions or inhalations of the drug are not included if there's no intent to abuse or if the adverse affect developed when the drug was used as prescribed. Also, accidental overdoses of OTC or Rx drugs taken as directed, unless used in combination with an illicit drug, are not included in the DAWN system. Also, alcohol is reportable only when used in combination with another drug.

We usually look at the number of emergency department mentions in this selected sample from DAWN. We look at prescription data, actual usage data, and we calculate a very simple frequency of use by the emergency

department over the number of prescriptions used in a certain time period. We chose for cyclobenzaprine two comparators of carisoprodol and diazepam because all three are centrally acting, they're available by prescription, they have sedating effects, and they also had the same therapeutic indication.

We see that the relative frequencies of reporting into DAWN for diazepam and carisoprodol are in the 10 to 11 range, and cyclobenzaprine close to 4. In the case of diphenhydramine, it's not a good comparator because of its availability being OTC, but we threw in a number of emergency department mentions just so that you see how diphenhydramine stacked up in emergency department submissions in this data set compared to the three muscle relaxants. I urge you to notice that we can't calculate the frequency of use because it being an OTC drug, we don't have actual usage data. But you see that diphenhydramine falls into the range between carisoprodol and diazepam in emergency department mentions.

Could I have the next slide, please?

Now, bearing that in mind, I thought that you might want to see how diphenhydramine stacked up back in our archival data, so I went back to some old DAWN data, also covering the same number of years, 1977 to 1982, so that you could get a perspective of how these three drugs

ranked back when diphenhydramine was available by prescription only. The emergency department mentions for diphenhydramine were one-tenth what they have been for the last six years of reporting. Diazepam is roughly the same, has roughly the same emergency department mentions, and carisoprodol was much lower at that time.

Could I have the next slide, please?

DAWN can be broken down by age, and you see that the 6 to 17 age range constituted 8 percent of these emergency department mentions, and by gender, 58 percent. Actually, that comes out to more than 100 percent, but it was 58 percent female and 42 percent male.

Next slide, please.

The reason for the emergency department visits were largely overdose, three-quarters of which were attempted suicides. The "Others" category, which came up to about 17.5 percent, included a whole gamut of reasons, including recreational abuse, accident, other psychic effects, and so on.

Next slide, please.

As you can see from this slide, most of the emergency department mentions resulted from cyclobenzaprine use in combination with other drugs. That's approximately 80 percent were in combination with other drugs, the majority of which the major drug in combination or the

substance in combination was alcohol. We show that there were other drugs of abuse that were also associated with cyclobenzaprine, and those are much smaller numbers that are on the slide.

Next slide, please.

For the medical examiner reports, we can see that the single drug episodes occur with a very low frequency. There were 146 total reports, of which only seven involved cyclobenzaprine used by itself, and the remainder in combination. Other drugs of abuse that were used in combination included alcohol, and other drugs of abuse are listed. They're also low level, but they included cocaine, marijuana, heroin and other opiates as well.

Next slide, please.

The Poison Control Center data provides data that can be used in addressing drug abuse that relates to exposure duration. Information is also provided for the reason for use, and it's broken down by age, the medical outcome, as well as a description of the clinical reasons for the Poison Control Center data.

Next slide, please.

In between 1986 and 1997, there were 31,000 Poison Control Center reports for cyclobenzaprine, of which approximately 17,000 were for use of the drug by itself.

More than 90 percent of these reports resulted from a single exposure over a short time period. So these were one-time events, as opposed to a drug such as heroin, which, if you have a report that involves heroin, you expect more chronic use on a regular basis. Intentional abuse and misuse combined was approximately 5 percent of these reports.

Next slide.

Suicide attempt was the most frequently reported reason for toxic exposure to cyclobenzaprine. Thirty-eight percent of the reports involved the drug in the suicide attempt as a single agent, and 53 percent were in combination with all other substances.

Next slide.

Eight percent of these suspected suicides involved minors, who were primarily teenagers, and that's for cyclobenzaprine in combination, and for cyclobenzaprine use alone, it was approximately 6 percent that involved minors.

Next slide.

The most serious medical outcomes for the drug alone. In this case, I'm just addressing the moderate effects and major effects because those are the ones that really required some sort of medical attention to varying degrees. The major effects may have had more long lasting

adverse consequences, and of course death. These comprised approximately 14 percent of the toxic exposures, and 3 percent of those involved minors. For all the reports, 21 percent of the toxic exposures were rated with the most serious medical outcomes, and 4 percent of these involved minors.

Next slide.

Again, the most serious medical outcomes involved combinations with alcohol and other drugs. So it was hypnotics, opiates, antidepressants, other skeletal muscle relaxants, and drugs of abuse. There were 39 deaths of all ages, total of all ages, and these were reported primarily for the drug and alcohol combinations again.

Next slide.

The primary clinical effects were neurologic, of which 68 percent were of the adverse effects reported were neurologic, the major one being drowsiness or lethargy, 44 percent. But these also included confusion, hallucinations, and the cardiovascular effects were about 16 percent of the reports, of which 13 percent were tachycardia.

Next slide, please.

AERS is the spontaneous reporting system of adverse effects. It comes in directly to FDA. This area is going to be discussed much more thoroughly in the

following talk by Dr. Neuner. We just looked at reports of drug abuse, drug dependence, and drug withdrawal as COSTART terms that would be reported to the system. There were approximately 9 reports of withdrawal and/or dependence. A couple of the reports were associated with depression. These may have been related to pre-existing conditions of the patients, and that sort of information on depression when it's pre-existing is hard to tease out from this sort of data system.

Next slide.

In conclusion, there is a signal of abuse and dependence from these systems. The major contributor to the signal is related to overdoses from suicide attempts, and approximately 8 percent of the suicide attempts occurred in minors. The relevance of these signals, the significance of them has to be taken in the context of the drug's safety features, its pharmacology, how it's going to be used in treatment, and other concomitant medications.

Thank you.

DR. BRASS: Dr. Yocum?

DR. YOCUM: In your ED department stuff, do you have any data on relationship to accidents such as motor vehicle accidents, fractured hip in the elderly, any sort of data that relates to some of the side effects that we're seeing?

DR. KLEIN: No. No, I'm afraid I don't, but we could go back over the system. In a case like that, that sort of information isn't tabulated individually, but the reports could be retrieved, with some difficulty.

DR. BRASS: Could you just clarify in the 39 deaths in the Poison Control data, were any of those with cyclobenzaprine alone?

DR. KLEIN: Three were.

DR. BRASS: Thank you.

Yes?

DR. LOVELL: You presented data on diphenhydramine when it went from prescription to OTC and it resulted in -- I think I heard you say a 10-fold increase in reports to your --

DR. KLEIN: Yes. I have to be very careful not to say that this event caused that 10-fold increase, because in the intervening time, there are a lot of changes, a lot of changes to the whole drug abuse scene, a lot of changes to the way people are taking drugs, and a lot of differences in the way a drug is recognized. So what I'm saying at this point is that to compare diphenhydramine now to those three muscle relaxants is not a very clean comparison because they're both available to different extents. But this is just to show you the perspective, that from that time period, that's what it

was.

I mean, we also see that carisoprodol is also much lower, and in the intervening years abuse reports of carisoprodol have increased. But that data is there. There's a 10-fold change in these number of reports, but to make the direct link as to what the cause was, I can't pull that out from the data.

DR. BRASS: Thank you.

Dr. Neuner?

DR. NEUNER: Good morning. My name is Rosemarie Neuner and I'm a medical reviewer from the Division of Over-the-Counter Drugs. For the next few minutes I will be discussing the findings of the Flexeril MR actual use trial and the safety review for this NDA.

Next slide, please.

My talk is comprised of data from the following sources: the results from the actual use trial and a safety review of the clinical study safety database, and postmarketing surveillance data from postmarketing studies, spontaneous adverse event reports, a search of the literature, and overdose data. I will not be discussing the latter since it has already been presented by my colleague, Dr. Klein.

Next slide, please.

I would like to begin my talk with the results

from the actual use study.

Next.

First I would like to start with some general background information about actual use studies. These studies simulate OTC use and usually have few exclusion criteria. Study objectives depend on the specific product and concerns related to that product such as compliance, dosing, duration of use, off-label use, safety and efficacy.

Next slide, please.

For Flexeril MR, there were two compliance issues that were studied in the actual use trial. They were: Are consumers able to follow labeling directions for appropriate dosing and duration of use for this product? Are consumers able to follow the warning statements regarding driving and the operation of heavy machinery while using this product?

Next slide, please.

The study itself was a multi-center, open-label, non-randomized, uncontrolled 7-day study in 468 adults with self-diagnosed painful muscle spasm, tightness or soreness of the back or neck. Recruitment for this study was done by a variety of public advertisements. Fifty-six percent of the participants entered in this study were recruited by newspaper ads.

Next slide, please.

Unlike other actual use studies, the Flexeril MR actual use trial excluded patients if they had a history of heart or thyroid disease, psychosis, substance abuse, concomitant treatment with sedatives, tranquilizers or anti-depressants, or if they had pending litigation or workmen's compensation for back or neck injury.

Next slide, please.

In this study, a 10-day supply of the drug was dispensed and used without physician intervention according to the listed directions, which read: "Take one tablet every six to eight hours. Do not exceed three tablets in 24 hours continuously for more than seven days." The study materials were collected from the participants on days 8 through 10.

Next slide, please.

The methods of evaluation used to assess patterns of use and participants' compliance with label directions were pill counts and the recordings from the participants' diary cards. The criteria used for determining non-compliance with the label instructions were as follows: If a participant took more than three tablets in at least one day; if a participant took more than one tablet per dose at least once, or if they medicated three times a day for eight, nine, or ten consecutive days.

Next.

Eighty-eight percent of the 468 participants entered completed the study. Twelve percent discontinued for a variety of reasons, such as adverse events, loss to follow-up, ineffective therapy, protocol deviations, never took therapy, or for other reasons. Ninety-six percent actually returned their diary cards and were included in the final study analysis.

Next slide.

The table on this slide shows that the overall compliance rate for the study was 73 percent. The sponsor also looked at the compliance rates of two other subgroups of participants, those who reported somnolence and those who had used the prescription drug previously. Individuals who had taken the drug previously tended to be more non-compliant, which means that they actually took more medication than directed.

Next slide, please.

This slide shows that the breakdown by reason for non-compliance for the three groups that were looked at in this study, as I have mentioned previously, this breakdown by reason for non-compliance shows that those who used the drug previously tended to be more non-compliant.

Next slide, please.

Analysis of the usage data revealed that 56

percent continued to take at least one pill for an additional three days, 13 percent took more than four pills per day.

Next slide.

After the study was under way, the sponsor added questions to assess the participants' adherence to the warning statements regarding not to drive or operate machinery. Thus, only 235 of the 449 participants were queried. This table shows that 60 percent of those questioned drove while taking this medication despite the warning not to drive.

Next slide.

The table on this slide shows that although only 29 percent of those queried operated machinery, 10 percent of them did not avoid doing so in face of the warning statements.

Next, please.

In conclusion, the actual use study's limited length makes it difficult to determine if there is a risk for potential misuse or drug abuse. The failure to heed the warnings regarding driving and operating heavy machinery is worrisome due to the drug's potential for sedation.

Next slide.

I will next discuss the clinical trial safety

database.

Next, please.

A total of 2,106 subjects were enrolled in the 13 trials. One thousand six hundred and thirty-two subjects actually took cyclobenzaprine. The duration of these trials ranged from 1 to 14 days. The majority of these studies were single-dose trials.

Next, please.

Demographically, the Phase III trials were predominantly Caucasian, female, age 30 to 39 years old. There were very few minority subjects enrolled in these studies. Only 5.3 percent of those who were treated with cyclobenzaprine were over 65 years of age.

Next, please.

Forty-eight percent of the cyclobenzaprine subjects reported one or more drug adverse events, as compared to 26 percent of the placebo subjects in these studies.

Next, please.

There was one reported death in the cyclobenzaprine group due to an acute MI. This occurred in a 33-year-old diabetic obese female after five days of treatment with cyclobenzaprine 5 milligrams three times a day, who developed shortness of breath and widened QRS complexes on EKG, which progressed to ventricular

fibrillation, cardiac arrest, and death. Autopsy revealed severe heart disease and measurable blood levels of a cocaine metabolite. Thus, this individual's death, due to an MI in the face of at least three known risk factors for heart disease, was confounded by the use of cocaine, which is a known arrhythmogenic agent.

Next slide, please.

The most commonly reported adverse events in the double-blind studies were somnolence, dry mouth, headache, asthenia/fatigue, nausea and dizziness. The incidences of somnolence, dry mouth, asthenia/fatigue and dizziness were found to be dose related compared to placebo.

Next, please.

It is important to note that the clinical trials submitted in support of this application were not designed to demonstrate possible adverse events due to drug-disease interactions such as glaucoma, thyroid or heart disease, prostatic hypertrophy, seizures, or drug-drug interactions.

Next slide.

Thus, no conclusions can be drawn from the safety database regarding subgroup analysis for risk of adverse events due to age and race. The risk for potentially developing drug-drug and drug-disease

interactions cannot be adequately assessed either.

Next.

The next part of my talk concerns postmarketing surveillance data associated with the use of prescription cyclobenzaprine.

Next slide, please.

The sponsor has resubmitted the data from two postmarketing studies with over 7,600 subjects, which has been previously reviewed by the agency. Overall, the safety profiles from these two studies were similar to that of the safety review database generated from the 13 clinical studies.

Next slide, please.

The sponsor has also submitted 968 postmarketing case reports of adverse events due to prescription cyclobenzaprine that they had collected up to August of 1998. Sixty-six of the 968 cases were due to drug overdoses. One hundred and eighty-six of the remaining 902 cases were classified as serious in nature. Fifty-one were death reports due to a variety of causes. There were an additional 35 deaths in the FDA's SRS database associated with the use of cyclobenzaprine that are currently under review.

Next slide, please.

The most frequently reported postmarketing

adverse events collected by the sponsor were mental disorder, hallucination, rash, somnolence, nausea, dizziness, confusion, and seizures.

Next, please.

Due to the limitations in time, I will only be discussing a few of these reports as related to drug-drug interactions. There were a total of 24 case reports of drug-drug interactions with cyclobenzaprine. Eight cases involved the use of alcohol, four cases involved the use of monoamineoxidase inhibitors, three cases involved the use of fluoxetine, an SSRI. The nine remaining cases involved a mixture of agents from various drug classes.

Next, please.

This NDA also contained the results of a worldwide literature search on cyclobenzaprine. One hundred and twenty-six publications from peer and non-peer-reviewed journals were submitted for a review, which included 25 case reports of a variety of adverse events such as neuroleptic malignant syndrome, torsades de pointes, seizures, drug-induced delirium, and tinnitus. There were also four articles expressing concern regarding the poor risk-benefit ratio of this drug in the elderly, who are at risk for developing adverse events due to the drug's anticholinergic effects.

Next slide, please.

Conclusions from the review of the postmarketing data are that risk does exist for drug-induced confusion, disorientation, hallucinations, and psychosis associated with the use of cyclobenzaprine. The risk for drug-induced adverse events cannot be assessed since drug interaction studies were not done.

Next slide, please.

Finally, the literature suggests individuals over 65 years of age may be at an increased risk for developing psychiatric disorders and CNS adverse events due to the drug's anticholinergic side effects.

Thank you.

DR. BRASS: Any questions for Dr. Neuner?

(No response.)

DR. BRASS: Thank you.

We will go on to Dr. Aikin.

DR. AIKIN: Good morning. My name is Kathryn Aikin. I am a social science analyst in the Division of Drug Marketing, Advertising and Communications. I'd like to talk to you today about the label comprehension study done as part of the application package for Flexeril.

Next slide, please.

Unlike prescription drugs, which are designed to be administered under the supervision of an alert intermediary, such as a doctor or other health

professional, consumers should be able to safely and effectively use over-the-counter drugs based solely on the package labeling. It is for this reason that the Code of Federal Regulations states that for OTC labeling to be clear and truthful, it must contain information on intended uses, directions, warnings, and side effects presented in a manner as to render the label likely to be understood by ordinary consumers, including individuals with low comprehension ability as assessed under customary conditions of purchase and use.

Next slide, please.

One way to assess consumers' understanding of the proposed labeling is to conduct a label comprehension study. A label comprehension study investigates the degree to which label communicates desired information. It usually involves measures designed to assess consumers' understanding of important label directions, warnings, and intended uses, and it's often conducted using a mall intercept methodology.

Next slide, please.

The label comprehension study for Flexeril focused on several main objectives: consumer comprehension of label directions, warnings, and uses; accuracy of consumer self-selection for use; consumer ratings of appropriateness of use for various pre-existing conditions;

and the package insert was also evaluated to investigate whether or not it affected comprehension of use and warning information. My talk today will focus just on the package labeling.

Next slide, please.

Four hundred participants were recruited. Participants who had suffered back or neck pain in the last 12 months and who had used prescription medication for back or neck pain sometime in the past or present were over-sampled. The sample included 102 participants aged 65 and over, and 48 participants who had not completed a high school education. The sample was equally divided by gender.

Next slide, please.

Participants were recruited in 14 geographically distributed malls across the United States. After being screened for eligibility, participants were provided with a picture of the front label of the product and given the following instructions: "Here is the front label for a new product you might see when you are shopping for nonprescription products. Please carefully look over the label and tell me when you are finished. Please take as much time as you need."

Next slide.

I'm sorry, go back one slide. Thank you.

After the participant had read the front label, the back product label was provided with similar introductory instructions. "Here is the back label from the same product. Please carefully look over the label as you would if you were going to consider buying this product for your own use. Please take as much time as you need and tell me when you are finished." The participant was then informed that questioning would focus on the back label. Both labels were left in front of the participant during questioning. The package insert was provided after participants had finished answering questions about the back label.

Next slide.

The results were analyzed by age, age 18 to 64 versus those 65 and older, and education level, those with less than a high school graduation versus those who had graduated high school or more. The significance level employed in the test was P or alpha, less than 0.10.

Next slide.

The results of the study can be divided into two areas, those concepts that were not well understood by participants and those concepts that were well understood. I will start first with the concepts that were well understood. There were a number that participants showed good comprehension on.

Ninety-six percent of participants understood that Flexeril can be used for back or neck pain due to recent muscle strain, 94 percent understood it could be used for neck or back pain due to recent muscle overuse, and 94 percent understood it could be used for spasm of the back or neck due to strain, overuse or injury. Participants understood many of the conditions that indicate a doctor should be consulted before taking Flexeril, including whether a person had heart, thyroid, or liver disease; pain shooting down the legs or back pain that gets worse when you lie down; weakness in an arm or leg; fever; difficulty urinating; taking sedatives, tranquilizers, antidepressants or other muscle relaxants; and if they were age 65 or older.

Next slide, please.

Participants understood there were drowsiness-related side effects associated with the use of Flexeril, and that alcohol, sedatives and tranquilizers may increase the drowsiness effect. This was assessed by agreement or disagreement with whether the statements "significant drowsiness may occur" and "alcohol, sedatives, and tranquilizers may increase the drowsiness affect" appeared on the label.

Ninety-one percent of participants understood they should take only one tablet at a time. Eighty-eight

percent of participants understood the maximum daily dose was three tablets in a 24-hour period. Eighty-eight percent of participants understood the product should be taken for no more than 10 days in a row.

Next slide, please.

There were some concepts that consumers did not show good comprehension on. Thirty percent of participants did not understand Flexeril works differently than a pain reliever. This includes people who said either that Flexeril works the same as a pain reliever or that they did not know how Flexeril worked. Participants aged 65 and older were more likely than younger participants to say they did not know how Flexeril worked.

Sixty-eight percent of participants did not understand that Flexeril can be taken concomitantly with pain relievers. Participants who did not graduate high school were more likely to get this wrong than those with a higher education. Forty-three percent of participants did not understand that Flexeril does not provide relief on the first day of use. These participants believed either that Flexeril provides pain relief within an hour or so, but then the relief wears off and could then come back. When asked to define the phrase what they thought "temporarily relieves pain, muscle tightness and spasm of the back or neck due to recent strain, overuse or minor injury" meant,

52 percent of participants said the pain is relieved in a few hours and then could come back, or the pain is relieved quickly. This is more descriptive of an analgesic. Both of these are incorrect in terms of how Flexeril works. These responses point to a pattern of understanding of Flexeril as a fast-acting analgesic and not as a muscle relaxant.

Next slide, please.

The percentage of participants who said they would use Flexeril for conditions they had previously experienced but were not indicated by label instructions ranged from 49 percent for neck pain to 79 percent for back and neck pain. The instructions on the label used indicate that Flexeril is only to be used for back or neck pain due to recent strain, overuse or injury.

Forty-two percent of participants aged 65 and over incorrectly indicate they would use Flexeril without first speaking to a doctor. Among participants age 65 and over, 28 percent indicated they would use Flexeril for arthritis in the knees, 40 percent indicated they would use Flexeril for back or neck pain caused by arthritis, and 49 percent indicated they would use Flexeril for leg cramps. None of these conditions are indicated by the label.

Next slide, please.

In conclusion, consumers generally understand

the dosing instructions. They understand to take one tablet at a time, no more than three in 24 hours, and for no more than 10 days in a row. Consumers generally understand that the product can be used for back or neck pain due to recent muscle strain, overuse or injury. However, they are less sure about conditions for which the product cannot be used, especially if they have experienced those conditions in the past.

Next slide, please.

Consumers age 65 and over may not consult a doctor before using the product. Consumers age 65 and over may use Flexeril for inappropriate conditions, such as arthritis in the knees and leg cramps.

Next slide, please.

Consumers may expect Flexeril to act like an analgesic. A large part of the sample indicated that Flexeril provides quick pain relief and that it works the same as a pain reliever.

In summary, there are concerns that consumers understand some but not all of the important label directions and warnings.

Thank you.

DR. BRASS: Thank you.

Are there any questions? Yes.

DR. LOVELL: In only one of the questions you

mentioned the differentiation between those with and without high school education.

DR. AIKIN: Yes.

DR. LOVELL: Can we assume from that that it didn't affect any other responses to the other questions?

DR. AIKIN: There were no differences on education in any of the questions that I mentioned. There were few differences between those with a lower education and a high education level on some of the other questions.

DR. BRASS: Dr. Andreason was supposed to present the FDA's presentation on neurologic impact. He's not available, so that presentation will be done by Dr. Katz.

DR. KATZ: I'm Dr. Linda Katz, Deputy Director of the Division of Over-the-Counter Drug Products. What I'm going to do is to go through Dr. Andreason's slides since he cannot be with us this morning. I would like to request, however, if anyone has critical questions regarding study design, if you can hold that to this afternoon since he should hopefully be available for our discussion time at around 2 o'clock.

Next slide.

What Dr. Andreason did was to review six studies to talk about the sedation and psychomotor potential of Flexeril. The major issue that comes about is

whether or not sedation may be a major therapeutic effect of the product itself, and if that's actually the way that it works. The question that was raised or addressed in all six of these studies was: Can Flexeril produce sedation without psychomotor impairment?

As I mentioned earlier, there were six studies that were performed. Three were two-hour post-dose studies, one was a study that explored peak pharmodynamic effects, and two studies compared Flexeril with other drugs at peak effect.

The order of the studies -- just follow with me because it's a little different than the review. Study 012 or 12 is the first one that I will talk about. The study objective was to measure the time course of sedation in Flexeril and comparative agents. This was designed as a double-blind, two-day, four-dose, placebo-controlled crossover study in 28 healthy volunteers. It compared the sedative effects of Flexeril, 5 milligrams taken three times a day, clemastine, 1 milligram BID, and diphenhydramine, 50 milligrams TID.

The study results indicated that the peak sedation occurred at approximately 4 to 6 hours post-dosing for Flexeril, and this was determined by the multiple sleep latency test. The peak sedation for diphenhydramine occurred at approximately two hours post-dosing. Further,

Flexeril 5 milligrams TID was found to be more sedating after the fourth dose or after the fourth hour until the end of the study, when it was compared to 50 milligrams TID of diphenhydramine. All active compounds caused some form of psychomotor impairment that roughly followed the time course of the sedation.

In conclusion for this study, Flexeril was found to be more sedating than diphenhydramine or placebo with repeated dosing; that the sedation and psychomotor effects occurred consistently; and the affects on psychomotor functioning was translatable to potentially impaired driving ability.

Studies 001, 002, and 003 are grouped together since their study designs are very similar. Study 001 was a double-blind, single-agent, crossover trial that was done with 24 volunteers. It was designed to compare the sedative and cognitive effects of Flexeril 2.5 and 5 milligrams with diphenhydramine taken three times a day. Study 002 was a double-blind, four-day, 10-dose, crossover study in 18 volunteers, again to investigate the sedative and cognitive effects of multiple doses of Flexeril, 5 milligrams TID. Study 003 was a double-blind, 4-day, 10-dose, crossover trial in 18 volunteers who were elderly, again with dosing TID, to investigate the sedative and cognitive effects of the multiple dosing of Flexeril, 5

milligrams, diphenhydramine, 50 milligrams, and placebo.

The assessment that was performed was the same in all three studies, and all studies employed self-report visual analog scales to assess subjective levels of alertness and mood, ranging from alert to drowsy.

A psychomotor testing was performed two hours post-dosing, and the assessments that were performed were for auditory sustained attention, delayed recall and recognition, finger tapping -- that one was not performed in 003 -- choice reaction time, critical flicker fusion threshold, which was also not performed in 003, continuous performance, visual sustained attention, digit span, and verbal free recall.

The summary of design and analysis power is basically seen in the next slide. The studies were felt to be underpowered. The sample sizes were fairly small and too small to conclude that there was no difference, that no difference means that there was no effect. The measurement affect taken before peak affect was reached in all of these studies. The statistical threshold for declaring no difference was too low in an analysis of safety.

The results showed that the impaired reaction time, total decision time, digit span reverse, which is I guess a compilation of memory and concentration, visual and sustained attention, all of these measures were impaired,

and Flexeril turned out to be more sedating than placebo.

In conclusion for these studies, studies 001 and 003 measured sedation and psychomotor function at peak effect time for diphenhydramine but not Flexeril. Studies 001 and 003 were felt not to be useful comparisons of Flexeril with diphenhydramine with respect to sedation or psychomotor function due to the sampling power sizes, as I mentioned earlier, and also to the problems with which the measurement times were taken.

Study 002 does not accurately measure Flexeril's potential for sedating properties, and despite the low power and off-peak effects, there was still significant drowsiness and psychomotor effects that were detected in all three of these studies.

Studies 014 and 015 are also put together since, again, their design is very similar. Both of these are double-blind, placebo-control, crossover trial that are single dose, and they were designed to investigate the effects of Flexeril, 5 milligrams, diphenhydramine, 50 milligrams, and amitriptyline, 50 milligrams, on driving-related psychomotor skills. The differences in these two studies were the populations that were studied. Study 014 looked at 32 volunteers that were age 65 through 82 years old, and in study 015 there were 32 volunteers age 21 through 40.

The assessments that were made in this trial were the visual analog scales, the divided attention task, also known as DAT, critical tracking task, CTT, vigilance task, VIG. In studies 014 and 015, psychomotor testing was performed 1 to 2 hours after diphenhydramine and 4 to 5 hours after Flexeril dosing. Driving simulators were not employed in any of these studies.

The results showed that critical tracking and vigilance were worse than placebo but roughly similar to diphenhydramine; that the impairment in psychomotor function occurred in the absence of perceived sedation in 014 for those individuals receiving Flexeril. The following is just a summary of the vigilance task with the response times and the errors that are seen in each of the groups.

As you'll see for diphenhydramine, the response time was 2.35 seconds, with an error of 16.5. For Flexeril it was 1.85, with errors that were 11.6.

In conclusion, Flexeril was found in these studies to be more sedating than placebo. Psychomotor impairment occurs in the absence of significantly perceived sedation.

The overall conclusions that were reached from these six studies were: sedation at night may be beneficial, but during the day it was be an adverse event.

Peak sedative and psychomotor impairment occurs 4 to 6 hours after dosing. Psychomotor impairment may occur in the absence of marked perceived drowsiness, and psychomotor impairment risk needs to be conveyed in understandable labeling terms.

DR. BRASS: Thank you.

Are there any questions for Dr. Katz?

DR. KODA-KIMBLE: This is not a neurologic question. Is it standard FDA procedure to use a P of 0.1 for safety?

DR. KATZ: For this kind of a trial -- and again, probably this question may be best answered by Dr. Andreason when he comes in, because these trial designs are designed a little differently than some of the trials we look at for safety and efficacy. But the 0.1 that was used is standard, to my understanding, of what Dr. Andreason has said. But I think if we could, could you defer that question to when he comes?

DR. KODA-KIMBLE: Sure. I think this is a question you can answer too. I believe the studies involved diphenhydramine 50 milligrams, and is it not true that the OTC dose is 25 milligrams?

DR. KATZ: It's 25 to 50.

DR. KODA-KIMBLE: Oh, okay.

DR. BRASS: Could you turn off your mike?

Other questions?

(No response.)

DR. BRASS: If not, thank you very much, and we will take our break now. We're a little bit ahead of schedule, so I'd like to reconvene at 10:10, if there's no objections.

(Recess.)

DR. BRASS: As we reconvene, if I could ask members of the audience who are here to present in the open public forum if they could be sure to touch bases with Dr. Titus during the lunch break so we have an accurate list of who has requested time in the open public forum.

I'd like to introduce Dr. Edwin Hemwall from Merck, who will lead the sponsor's presentation.

DR. HEMWALL: Good morning, advisory committee members, FDA staff, guests. I'm Ed Hemwall, representing Regulatory Affairs for Merck Research Labs and Johnson & Johnson-Merck Consumer Pharmaceuticals. We're here today to present the results of our development program which formed the basis for our conclusion that Flexeril 5 milligrams available in nonprescription form will offer a safe and effective treatment option for millions of Americans who suffer from occasional muscle spasm or strain of the back or neck.

Back problems are a common medical condition in

the United States. By one measure, approximately 15 million adults report disabling low back pain each year. Approximately 50 percent will self-medicate before consulting a primary care physician, and another study concludes that roughly 60 percent of the people with acute episodes will suffer a recurrence within one year. So it's clear that back pain is something that affects the daily lives of a large number of the American public, and these numbers don't even include the chronic conditions or pain from other regions of the back or neck.

Indeed, it's probable that most of you in this audience have either suffered from acute back pain or know someone who has at some time or another. Thus, it should not really be surprising that over 30 million prescriptions are dispensed each year for drugs in the muscle relaxant category.

Within that muscle relaxant category, the most commonly prescribed product is Flexeril or its generic equivalent, cyclobenzaprine hydrochloride. Flexeril has been available by prescription in the United States, as you heard, since 1977 at a recommended dose of 10 milligrams three times daily. As you know, it's indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute painful musculoskeletal conditions. Despite being available generically since

1989, and therefore not promoted, the use of cyclobenzaprine has continued to increase to a current rate of over 10 million prescriptions per year, and this continued growth provides a measure of the reliance and the value that physicians place upon this product as safe and effective treatment of this common medical condition.

The idea that Flexeril or other muscle relaxants would be reasonable for OTC availability has often been considered, as you heard this morning. In fact, the muscle relaxant category is a new concept in the U.S., but the general concept of treating muscle pain as an indication for treating back pain or spasm is not. Millions of Americans purchase a variety of NSAIDs, non-specific analgesics, topical balms, and yet still find it necessary to visit a physician to obtain access to the more effective relief from prescription-only medications.

Several muscle relaxant drugs, not including cyclobenzaprine, have been available over-the-counter in Canada for over 20 years. In fact, they were reevaluated in 1995 and were moved from a more restrictive, behind-the-counter, third-class to the more open, front-of-the-counter status in all the provinces, attesting to a history of consumer safe self-medication of common back problems.

As you also heard this morning, in 1995 your predecessors on these two advisory committees spent an

afternoon discussing in general terms the pros and cons of OTC availability of this diverse range of drugs in this category, and during those deliberations, certain key considerations or challenges were identified for sponsors seeking to develop a nonprescription version of a muscle relaxant drug, and these included proof of efficacy that is not only statistically significant but clinically meaningful, establishing a safety profile that is consistent with and appropriate for OTC use, and demonstrated consumer ability to use the product correctly.

One of the committee's recurring observations, however, was the lack of quality data to address these questions. We listened to those concerns, and the Flexeril OTC development program, which includes 13 clinical trials, was carried out to address these issues and others specific to cyclobenzaprine. Today we're pleased to be able to review for you compelling new findings which establish for the first time a data-driven foundation for considering OTC use for a muscle relaxant product.

The effectiveness of the 10 milligram prescription dose of cyclobenzaprine has already been established and validated by over 20 years of clinical use. In order to establish efficacy of the lower 5 milligram dose in the OTC indication, we conducted two large multi-center placebo-controlled studies in patients with painful

muscle spasm of the neck or low back. Beyond satisfying the primary endpoint success criteria from patient self-assessments, data from these studies addressed the other questions which are on your mind of dose response, time to the onset of relief, physician-verified reduction of palpable muscle spasm, the role of sedation in efficacy, and the magnitude of the treatment effect.

In order to assess safety as it applies to OTC availability of the lower 5 milligram dose, we examined all clinical studies databases for all doses. We also examined the extensive marketed use experience with the 10 milligram prescription dose, including nonprescription spontaneous adverse event reports from over 100 million prescriptions dispensed over 20 years, and two postmarket surveillance studies in over 7,600 patients, safety in overdose, both alone and in combination with other agents, and the potential for abuse or recreational use.

In addition, as you heard this morning, we conducted four clinical pharmacokinetic studies, six special clinical pharmacology studies designed to assess the sedative properties of the lower 5 milligram dose relative to other OTC drugs and whether or not that sedation or drowsiness translated to impaired psychomotor function in both young and elderly subjects.

Finally, a key component of any Rx to OTC

switch program is demonstrating the ability to use the product correctly in a simulated OTC environment. We developed multiple sequential iterations of the draft label with FDA input at various stages along the way. As you've already heard, our program included a pattern of use study in which patients with self-diagnosed painful muscle spasm, tightness or soreness of the back or neck, were given a 10-day supply of the product and instructed to take it according to the label.

Additionally, we performed a comprehension study from which we applied the learnings to improve the final proposed label provided in your background package, and this study assessed the ability of the carton back panel and package insert to communicate key label messages, such as how and when to use the product, who should or should not use it, when to see a doctor, the potential to cause drowsiness, and the delayed onset of action.

The proposed indication or use for the 5 milligram dose is for relief of painful muscle tightness and spasm of the back or neck due to a recent strain, overuse, or minor injury. One tablet should be taken every 6 to 8 hours; no more than three tablets daily for no more than 10 days duration. A range of additional information including warnings is also provided, some of which are standard OTC labeling language. Much, however, is unique

to the use of the Flexeril product and its attributes, and as noted, it has been substantially enhanced to address the shortcomings of the version that were seen in the comprehension study, as reviewed by Dr. Aikin.

As stated earlier, label development is an interactive process, and we look forward to continued collaboration with FDA experts to further improve the labeling for this new category.

So, to summarize, in the presentation that Dr. Scott Korn will provide today, you will see that we do have a strong rationale for proposing OTC availability for Flexeril product, and you will see that we have addressed the important questions, perhaps even some misunderstandings that have existed before now, and we believe that our program has demonstrated clinically meaningful and statistically significant efficacy of the lower 5 milligram dose in the target OTC population. We have provided an extensive safety profile from over 20 years of prescription use of the 10 milligram dose, and from new studies of sedation potential which are consistent with and acceptable for OTC availability.

Finally, we have produced a basis for informative labeling which enables consumers to safety self-treat this common medical condition.

We have the following independent consultants

with expertise in several topics today to provide additional perspective on some of the questions which may arise during your deliberations: Dr. Moore, a rheumatologist and former member of the Arthritis Drugs Advisory Committee; Dr. Borenstein, a rheumatologist and expert in back pain management; Dr. Preskorn, clinical psychiatrist and expert in pharmacokinetic/pharmacodynamic relationships; Dr. Wilkinson, the lead investigator in the driving skills psychomotor studies; Dr. Lesser, a neurologist and expert in the study of seizures; Dr. Barbey, a cardiologist and clinical pharmacologist and expert in drug electrophysiology; Dr. Jones, formerly of the FDA and expert in pharmacovigilance; and Dr. Koch, an expert in clinical trial design and statistics.

The concludes my introduction. I'd now like to introduce Dr. Scott Korn from Merck Research Labs Clinical Research. Dr. Korn will review with you the most important features of our OTC program, which is covered in much greater detail in your background information package.

Thank you.

DR. KORN: Good morning. As Dr. Hemwall stated, the nonprescription cyclobenzaprine program had three primary objectives. First, to evaluate the efficacy and safety of cyclobenzaprine in doses of less than 10 milligrams. Second, to evaluate the potential of the

proposed OTC dose to impair performance. Third, to develop and test a label that could clearly convey the key information required for safe self-medication.

This morning's presentation will review the efficacy, then pharmacokinetic, then safety, then label development studies. In each section, I will highlight data that is pertinent to the questions that you have been asked to discuss this afternoon.

Protocols 6 and 8 were the two pivotal trials, and they examined the following two questions. First, is there a dose less than 10 milligrams that is effective and less sedating than the 10 milligram dose? We recognized that the proposed OTC dose should be statistically different than placebo and provide a clinically significant difference as well. We also wanted to examine in these studies whether the proposed OTC dose actually reduces palpable muscle spasm as evaluated by a physician.

The two trials had similar designs. Both were double-blind, randomized, placebo-control. In Protocol 6, we have included the 10 milligram dose, the proposed OTC dose of 5 milligrams, and placebo. Protocol 8 was conducted after Protocol 6 already showed that 5 milligrams was effective, so we did not include the 10 milligram dose but instead put a 2.5 milligram TID dose in to better characterize the entire dose-response curve for efficacy.

In both trials patients with acute physician-rated moderate or moderately severe spasm were enrolled. Concomitant analgesics and nonsteroidal anti-inflammatory drugs were prohibited during the two trials.

This schematic shows that patients had three office visits during the study, on Day 1 when they were randomized to medication, on Day 3 or 4 which was their first on-treatment evaluation, and on Day 8 after they had completed 7 days of medication. There were two rating scales that the patients completed at Visits 2 and 3, their on-treatment visits, and there was a diary that patients filled out each evening that included one rating scale.

Dr. Witter reviewed the rating scales this morning. Each of them was a 5-category scale. The clinical global impression of change and medication helpfulness scales were completed at the office visits. The relief from daily backache question diary was completed each evening. On each of the 5-category scales, we predefined that the top three scores would be considered responders, and the lower two scores would be considered non-responders for our secondary analysis of responders.

We predefined what the criteria would be for a successful treatment. At either Visit 2 or at Visit 3, an effective treatment needed to be significantly superior to placebo for two of the three patient ratings, namely the

clinical global impression of change, the medication helpfulness, or the patient's daily diary. We prespecified that the treatments would be compared using a P value of less than or equal to 0.03 to provide an overall alpha level for the experiment of 0.05 or less.

Protocols 6 and 8 had similar patient demographics. Patients were slightly more females than males, mean age approximately 42, predominantly Caucasian. About two-thirds of the patients had low back pain and one-third had neck pain. By design, the two studies differed in the duration of symptoms before randomization. In Protocol 6, patients were allowed to be symptomatic for up to 14 days before entry. In Protocol 8, we wanted more acute patients, so we limited enrollment to patients who had been symptomatic for less than 7 days.

We see on this slide the primary results from Protocol 6 for the three primary endpoints. The means for each of the three parameters are shown. We notice in the far-right column that cyclobenzaprine 10 milligrams was significantly different than placebo, as indicated by the asterisks, for each of the three parameters at each of the two primary time points for each parameter. So cyclobenzaprine 10 milligrams was clearly effective according to the predefined criteria.

Cyclobenzaprine 5 milligrams was also clearly

effective, being statistically significantly different than placebo in each endpoint at each of the primary time points. The only difference between the 5 and the 10 milligram dose was that the 5 milligram dose, as expected, had slightly slower onset of action than 10 milligrams. At the primary time points, however, the means for 5 and 10 were virtually identical.

This slide displays the results of Protocol 8 in the same format. This study confirmed that 5 milligrams is an effective dose. Looking at the far-right column for Protocol 8, 5 milligrams was significantly better than placebo for each of the primary endpoints at the final visit of the study. In contrast, 2.5 milligram dose was only significantly better than placebo on one of the parameters at one of the time points. So Protocol 8 confirms that 5 milligrams is effective.

The difference between 5 milligrams and placebo was consistent across the two trials. The mean relief from starting backache for 5 milligram and placebo are shown on this slide from both studies. The diary ratings show that the relative efficacy of 5 milligrams was similar in the two trials. The placebo response on Day 2 in the second trial was slightly higher, and that probably explains why the differences between 5 milligrams and placebo were significant at Visit 2 in Protocol 6 but not in Protocol 8.

In order to examine whether the difference from placebo was clinically meaningful in addition to statistically significant, we conducted three secondary analyses. The first analysis was time to any patient reported in their diary that they had a lot or complete relief, what I'll call substantial relief. This slide shows the cumulative proportion of patients who recorded in their diary that they had a lot or complete relief by study day in Protocol 6. The 5 milligram group in the yellow color and the 10 milligram group in the pink color had significantly different distributions than did placebo. The median time to a lot or complete relief with 5 milligrams and 10 milligrams was approximately 5 days, and that was about 2 days less than with placebo. Two days in a 7-day period is clearly a clinically meaningful difference, since the sooner a patient gets pain relief, the sooner they should be able to resume their normal activities.

This slide shows the same analysis for Protocol 8, and the results are similar. The 5 milligram group in the yellow was significantly different than the placebo group in the white, and the median time to a lot or complete relief was approximately 2 days less with 5 milligrams than with placebo.

The second analysis we conducted concerned the

magnitude of effect looking at the difference in the proportion of responders between the 5 milligram group and the placebo group. In Protocol 6, the differences in the proportion of responders between 5 milligrams and placebo ranged from 11 to 17 percent. The advantage for 5 milligrams relative to placebo was as large as the difference between 10 milligrams and placebo, and both differences for 5 and 10 are large enough to be clinically meaningful.

The difference that we see in this slide is actually very similar to the order of magnitude that has been shown with the H2 blockers in their nonprescription studies for heartburn relief.

Looking at Protocol 8, we see the same phenomenon. On 5 milligrams relative to placebo, the 5 milligram group had a 12 to 20 percentage point increase versus placebo. In contrast, the 2.5 milligram group generally had a less than 10 percentage point difference versus placebo.

The third analysis we performed was to place the observed differences in a clinical context by calculating the standardized difference from placebo, otherwise known as effect size. This is defined as the difference in means divided by the pooled standard deviation for all the treatment groups in the trial. It's

a unitless measure that can be used to provide a common metric for comparing drugs within and across studies. The values for 5 milligrams in both of our trials ranged from 0.24 to 0.41, which is modest but consistent with the other analyses that I've just presented.

These values actually compare quite favorably with published values for antihistamines used to treat symptoms of the common cold. In a published meta-analysis, the pooled estimate for the antihistamine effect was 0.153 to 0.291, which is, if anything, a little less favorable and less robust than the difference for cyclobenzaprine.

So the analysis of effect size was the third analysis that showed that the difference between 5 milligrams and placebo was clinically meaningful.

We predefined in a planned combined analysis of Protocols 6 and 8 to look at whether sedation was required for efficacy. In Protocols 6 and 8, there were 321 patients who received 5 milligrams and did not report sedation at any point during the trial. There were also 412 patients in those trials who received placebo and did not report sedation. The display on the screen here shows the proportion of responders for the clinical global impression of change rating at Visit 2. Three values are shown for the 5 milligram group and three values are shown for placebo. For 5 milligrams, we see the point estimate

for percent of responders for all patients, those 321 who did not report sedation and the 132 who reported sedation. For placebo, the same three subgroups, all patients and those who did not report sedation.

Looking at the proportion of responders, we see that the difference between 5 and placebo in those who did not report drowsiness is as large as the difference between 5 and placebo in the all patients treated analysis. To us, this demonstrates that clinically apparent sedation is not required for the product to be effective. Efficacy is not a result of just inducing drowsiness.

Turning our attention to the physician ratings, at each of the visits the patients were examined and their muscle spasm was rated by a physician using this 5-category scale that was based on the hardness and consistency of the muscles. Patients had to have a score of 2 or 3 to be randomized into the trial, a rating of moderate or moderately severe.

A secondary analysis specified in our protocols was to look at the degree of reduction in muscle spasm at the follow-up visits. This slide summarizes the mean muscle spasms by treatment group and visits in the two protocols. At baseline, the treatment groups were similar. In Protocol 6, at both Visit 2 and Visit 3, both 5 and 10 milligrams had significantly less spasm than did placebo.

In Protocol 8, the 5 milligram group had significantly less muscle spasm than placebo at Visit 3, while the 2.5 milligram group did not.

So both trials demonstrated that, according to physician examination, a greater reduction in muscle spasm occurs with 5 milligrams than with placebo.

One of the questions you've been asked to consider this morning is whether patients can tell that their condition is improving. We looked at the correlation between the physician ratings of muscle spasm and the patient global ratings that were the primary endpoints in this trial. There was an appreciable correlation between the physician ratings of spasm and the patient global ratings. The Spearman correlation coefficient summarized on this slide ranged from 0.297 to 0.644. These correlation coefficients show that patients with acute painful muscle spasm of the back or neck can indeed assess whether their spasm is improving.

Another question that you've been asked to consider today is what is the evidence that patients can self-diagnose this condition. We went back and looked at the screening logs from the sites in the two studies to help address this question. Fourteen of the 20 sites in Protocols 6 and 8 included the phrase "muscle spasm" in advertisements that were used to recruit patients. Looking

at those 14 sites, there were 439 patients who were screened, and of those 439 patients, only 6 percent were excluded from the studies because they did not have cervical or lumbar muscle spasm on examination. This data indicates that patients who respond to advertisements for patients with muscle spasm do indeed have physician-confirmed muscle spasm when they're enrolled in the trial.

The data we have reviewed from Protocols 6 and 8 demonstrate that cyclobenzaprine 5 milligrams TID are statistically and clinically superior to placebo for acute painful muscle spasm of the back or neck. The overall efficacy of 5 milligrams TID is similar to 10 milligrams TID, examining the mean scores at the primary time points. The only difference is that 10 milligrams has a faster onset of efficacy, as you would expect.

Muscle spasm has been shown to resolve more quickly with both 5 and 10 milligrams TID than with placebo, and patients can indeed recognize when they have painful muscle spasm, and they can accurately determine whether that condition is improving with treatment.

Turning our attention to safety, at therapeutic plasma concentrations of cyclobenzaprine, we know there are two pharmacologic effects. The first is an antihistaminic effect on the H1 receptor, and the second is an antimuscarinic or anticholinergic effect. As we examine

the safety data from our clinical trials, we will see that the clinical adverse experiences reported are consistent with both of these known pharmacologic effects of the drug.

Since safety can be influenced by pharmacokinetics, I will review what we know about the kinetics of cyclobenzaprine first, and I will then discuss the safety data from our nonprescription clinical studies, both the adverse experience data and the psychomotor data that Dr. Katz presented. I will then review the information from the marketed use of the 10 milligram product, and that includes the spontaneous reports to Merck or the FDA, the Poison Control Center data, and the Drug Abuse Warning Network data.

The pharmacokinetics of cyclobenzaprine have been examined in earlier studies, as well as part of this nonprescription development program. As Dr. Lee presented, the drug is well absorbed, it has a high clearance, a large volume of distribution, and it is highly protein bound. The Tmax is reached in four hours, and after 7 days of dosing TID, the plasma concentration at steady state in younger subjects is about four-fold higher than a single dose, and in elderly subjects about eight-fold higher than after a single dose.

This is a slide similar to what you've been shown this morning. There are three treatment groups on

the slide, 5 milligrams TID in the yellow. In the elderly patients, 65 to 79 years old, it's a closed square. In the younger patients, 22 to 40, it's a closed circle. We see that after a single dose, the levels in the elderly and the young are similar after 5 milligrams, and peak concentration is approximately half of that after 10 milligrams. Looking at steady state after 7 days of dosing, a slightly different picture. In the young, this is the plasma concentration at steady state. The elderly patients who have 5 milligrams TID develop plasma concentrations that are similar to younger subjects who take the current prescription dose of 10 milligrams TID.

Now, we have submitted the information to the agency for our prescription product as well, and we have submitted draft labeling incorporating this revision and the hepatic impairment data, and we look forward to the agency's review of that data and approval to change our current prescription circular.

As Dr. Lee mentioned, there was a radiolabeled oral study done as part of the original NDA over 20 years ago. Approximately 50 percent of the drug was observed to come out in the urine. The major fraction in the urine was a glucuronide. There were four oxidative metabolites identified, each about 3 to 7 percent of the total radio activity, and those were mediated through several P450

isozymes, 3A4, 1A2, and 2D6. There were also a number of unidentified low concentration metabolites and one that's approximately 6 percent.

We reviewed this data and we believe that the drug has a low potential for drug-drug interactions. First, it is unlikely that other drugs will significantly exhibit the excretion of cyclobenzaprine since there are multiple elimination pathways. There's fecal excretion of unchanged drug, there's urinary excretion of a glucuronide, and there's oxidative metabolism using several different enzymes. We also have in vitro data that shows that cyclobenzaprine does not inhibit the major P450 isozymes, although we do not have that data for 2C19. So it's unlikely to inhibit the metabolism of other drugs that rely on 3A4 or 2D6.

We have had extensive marketed experience with cyclobenzaprine, and there are no documented pharmacokinetic interactions reported in the literature. What I mean by documented is there are no case reports where the plasma concentration of either cyclobenzaprine or another drug was shown to have been altered by concomitant administration.

I'd like to now turn our attention to the clinical adverse experience profile. Information about adverse experiences was collected by open-ended questioning

in all of our studies. Merck defines an adverse experience as any unfavorable clinical event, whether or not it is considered related to the study medication. The event only needs to occur once during the trial and it is counted as an adverse experience. At the end of the trial the investigator is asked to assess the relationship to study medication for any events that have been reported.

The most commonly observed adverse experiences with 5 milligrams in Protocols 6 and 8 are presented on this slide. We see that the incidence of adverse experiences is clearly dose related, ranging from 35 percent on placebo to 44 percent on 2.5, 55 percent on 5, and 62 percent on 10 milligrams administered TID for seven days.

The most common adverse experiences were drowsiness and dry mouth, which are both reflections of the antihistaminic and anticholinergic properties of the drug. Approximately 29 percent of the patients who received 5 milligrams reported drowsiness, and this compared to approximately 10 percent of the patients who received placebo. Twenty-one percent of the patients who received 5 milligrams reported dry mouth, compared to approximately 7 percent of the patients who received placebo.

Asthenia and fatigue, which are terms used by some investigators to describe drowsiness or related

experiences, also appear to be dose related, ranging from 2.6 up to 6 percent.

Headache and nausea were not dose related, and indeed the incidence of headache and nausea with 5 milligrams were actually less than with placebo.

While 55 percent of the patients who received cyclobenzaprine 5 milligrams reported one or more adverse experiences, very few discontinued medication because of an adverse experience. This slide summarizes the discontinuations due to adverse experiences in the Phase III studies, including the 469-patient use study. Discontinuations due to adverse experiences were dose related. We see them ranging from 1.6 percent on placebo up to 7.5 percent on 10 milligrams. Four percent of the patients who received 5 milligrams discontinued for an adverse experience, versus 7.5 percent of the patients who received the current prescription dose.

The most common adverse experience prompting discontinuation was somnolence. Two and a half percent of the patients who received cyclobenzaprine 5 milligrams discontinued the medication because of somnolence.

The investigators were asked to rate the intensity of all adverse experiences on a 3-point scale: mild, indicating that the patient was aware of the symptom but it was easily tolerated; moderate, indicating that the

symptom may have interfered with the patient's usual activity; and severe, which is the inability to work or do the patient's usual activity.

We see on this slide a chart illustrating the maximum intensity of somnolence at any point for patients who received 5 milligrams in Protocols 6 and 8. Seventy percent of the patients did not experience any somnolence. Seventeen and a half percent said the worst their somnolence was was mild, 9.3 percent said they had moderate drowsiness at some point, and only 2.4 percent reported that their drowsiness was severe enough to interfere with their daily activities at any point during the study.

When did the somnolence or drowsiness start in these patients? The proportion of patients who received 5 milligrams TID and first reported somnolence on a given day is displayed on this slide. We see that approximately 16 percent of the patients reported drowsiness starting on the first day, and an additional 10 percent reported drowsiness beginning on the second day. But from the third day on, very few patients reported the onset of somnolence. So based on this data, we conclude that when somnolence occurs, it generally starts on the first or second day of dosing.

One might expect that elderly patients would have more adverse experiences than younger patients given

that their plasma concentration for an equal dose would be higher, but our clinical data does not show that. In the Phase III studies, the incidence of adverse experiences in the 74 patients age 65 and older was not greater than in the patients who were less than 65 years old. This slide displays those adverse experiences that were reported by two or more of the patients who were 65 years old. The incidence of somnolence in the elderly patients was not different than in the younger patients. The incidence of dry mouth and constipation and abdominal pain did appear to be slightly higher, and these are reflections of the anticholinergic properties of the drug.

As Dr. Neuner discussed, many patients use cyclobenzaprine for up to 10 days in the use study. So based on the safety data from that use study and our two pivotal trials, we've concluded that cyclobenzaprine 5 milligrams TID is generally well tolerated when used for up to 10 days. Somnolence and dry mouth are the most common adverse experiences, and they are both dose related. Most patients who reported somnolence develop it on the first or second day of dosing, but most episodes of somnolence are mild or moderate and do not prompt discontinuation of the treatment.

In order to better understand the characteristics of the drowsiness that can occur with

cyclobenzaprine and whether it leads to impaired performance, we conducted six psychomotor studies, two of which were in elderly subjects. An alert/drowsy visual analog scale was used in all six studies to assess the subjective sensation of drowsiness, and one study included the multiple sleep latency test. We included computer-based measures of psychomotor performance in all trials, and although our package warns against driving until you know how the product reacts with you, we know that some people will drive while taking a potentially sedating medication, and therefore we did two studies designed to specifically address the extent to which cyclobenzaprine 5 milligrams could impair driving-related skills. In answer to Dr. Koda-Kimble's question, we were not aware at the time the studies were planned or conducted that they would be evaluated at a P value level of 0.1.

The first four trials were basically exploratory in nature. What we learned from these studies is that cyclobenzaprine 5 milligrams is more sedating than placebo in subjects who are less than 50 years old. The onset of sedation occurs later than with diphenhydramine. Peak sedation with cyclobenzaprine is approximately four hours post-dose, and with diphenhydramine it's approximately one to two hours post-dose. Of interest in our multiple-dose studies, we did not see sedation continue

to increase over the course of 10 doses.

The MSLT study, or multiple sleep latency study, did demonstrate that cyclobenzaprine reduces the amount of time it takes to fall asleep in an unstimulated environment when you're told to try and fall asleep, and it does so by about one to two minutes more than the maximum OTC dose of either diphenhydramine or clemastine, which is known as Tavist. In all four studies, however, there was no consistent impairment either at 0.05 or at 0.1 of substantial psychomotor impairment.

We took the results of these four trials and we then designed the two trials that looked specifically at driving-related skills. We designed those studies to assess psychomotor performance at the time when maximum sedation would be expected based on the results of these four exploratory trials.

We conducted the two studies, one in the elderly, age 65 and older, and one in subjects age 21 to 40. Both are summarized in your background package. I will in the interest of time only present the results of the elderly since those subjects are assumed to have had higher plasma concentrations than the younger subjects and would be expected to have, if anything, greater impairment. Both trials were double-blind, 4-period crossover studies. The subjects received three doses of cyclobenzaprine on Day

1 and the fourth dose the morning of Day 2, four hours before the test battery was begun. They also received in the other periods amitriptyline 50 milligrams, diphenhydramine 50 milligrams, and placebo.

We selected amitriptyline as the positive control based on the extensive information available in the literature that it indeed is associated with impairment in test batteries like this, and actually an increased risk of traffic accidents in epidemiologic data. Diphenhydramine was included to evaluate how cyclobenzaprine compares to a currently marketed OTC antihistamine.

Subjects completed a visual analog scale at the beginning of the test battery, and then three driving-related tests were conducted. Now, this test battery was selected instead of a driving simulator as it has been well validated over the years. It is a multidimensional test battery that has evolved from over 25 years of laboratory work by the investigators and has been shown to be sensitive to the effects of alcohol, drugs, and aging. Skills impairment in this battery mirrors the blood alcohol concentration curve and its relationship to crash risk. The battery has an excellent test/retest reliability, and it produces results that are consistent with a state of the art driving simulator as was recently shown in a study by the investigators for the Department of Transportation.

I will explain what the three tests are and then show the relevant primary endpoint data for each of the three parameters.

The first psychomotor test is critical tracking, which is the ability to control movement of a machine in use during very focused brief periods of attention. The test consists of a subject trying to follow a cursor on a computer monitor by using a joystick. The cursor moves more and more quickly as the trial progresses, and it becomes more and more difficult to follow with the joystick. The primary parameter in this study is the lambda score, which is the level of difficulty the subject is able to complete. So a higher score is a higher level of difficulty and represents less impairment.

The mean lambda score and the 95 percent confidence interval is shown for each of the treatment groups in this slide. We see amitriptyline on the far right has the worst level of performance, and placebo on the far left had the best. Cyclobenzaprine was significantly different than placebo, but the difference is quite small and actually is less than 10 percent and not significantly different from the level of diphenhydramine in this test parameter.

The second test was divided attention, which models the demands of driving on a highway. It's the

ability to simultaneously perform tracking, which you can think of as steering, and visual searching, which is looking to the sides of the vehicle. When you do the visual searching, you're monitoring for cues that require a response. This is a very complex, high-demand task, and it's a very good analog for driving.

The primary parameter for this test is an overall performance score which incorporates a measure of tracking error or weaving and response time to a visual signal, reaction time.

The overall performance score and 95 percent confidence interval for each treatment are shown on this slide. The data is normalized to a score of 50, so a lower score in this parameter indicates less impairment. Amitriptyline on the far right had significantly more impairment than placebo. Cyclobenzaprine and diphenhydramine were not significantly different than placebo, and cyclobenzaprine was not significantly different than diphenhydramine either.

The third test is vigilance, which is the ability to maintain attention to a monotonous task over 40 minutes in a sound-proof booth. This is actually the opposite of the MSLT test, where subjects are told to fall asleep as fast as they can. Here the subject is told to stay awake during the monotonous period in the booth. The

primary parameter in this test is the reaction time to an infrequently appearing signal, and the higher score or the higher reaction time represents more impairment. So while they're in the booth, there's a signal that appear intermittently and they're supposed to react and indicate that they've acknowledged that signal when it occurs. So a higher reaction time is worse.

A secondary parameter for this test is actually the number of errors, either the number of times they've missed a signal and did not acknowledge it, or the number of times they acknowledged a signal that actually never occurred.

The mean response time in seconds and the 95 percent confidence interval are shown on this slide. Amitriptyline and diphenhydramine had significantly prolonged reaction times compared to placebo, while cyclobenzaprine was not associated with a significant increase in reaction time. The 1-second difference between amitriptyline and placebo may not look like a lot on this slide, but if we remember that a car traveling 55 miles an hour travels 80 feet in that one second, a 1-second prolongation is clinically meaningful.

A secondary endpoint in this trial was the number of errors, the signals they missed or the signals they acknowledged that weren't there. Here we see that

amitriptyline and diphenhydramine and cyclobenzaprine were associated with more what we'll call false alarms or signals received that weren't there than was placebo, but clearly cyclobenzaprine is not as bad as amitriptyline, and cyclobenzaprine is not significantly worse than diphenhydramine.

The driving-related skills study in the younger subjects showed even smaller differences than these that were seen between cyclobenzaprine and placebo in the elderly subjects. Based on all six psychomotor studies, we conclude that cyclobenzaprine 5 milligrams TID is associated with sedation that is similar to that seen with OTC doses of diphenhydramine and clemastine as measured by a visual analog scale. Cyclobenzaprine 5 milligrams does assist in falling asleep when someone is trying to do that, but it does not substantially interfere with critical driving skills either in young or elderly subjects to a substantial extent. Subjects can generally overcome their drowsiness and perform adequately in these laboratory studies. In both the young and the elderly, performance in the laboratory study was not worse than with the maximum OTC dose of diphenhydramine.

I would now like to move on to the next section of the talk which deals with what we know about the safety of the 10 milligram product that's been marketed since

1977. Merck conducted two open-label postmarketing surveillance studies. These enrolled approximately 7,600 patients, and 567 of those patients were 65 years old or older. The elderly patients in these two studies did not have a higher incidence of adverse experiences than the younger patients. Approximately 20 percent of the elderly patients and 19 percent of the younger patients reported an adverse experience in these large trials conducted 20 years ago. Looking at the profile of adverse experiences, they were generally similar in the elderly to the younger groups.

Merck collects spontaneous reports of adverse experiences on all of its products and enters that data in a database that we refer to as our Worldwide Adverse Experience System. All voluntary reports to Merck of adverse experiences after use of a Merck product are entered into this database regardless of whether the reporting physician or a company physician feel that the case is causally related to the product.

It's worth noting that reporting practices have changed since 1977. The terminology of adverse experiences used by both us and the FDA has changed over that time, and the regulatory definition of what is a serious adverse experience has changed over time.

We estimate that since 1977, physicians have

written over 100 million prescriptions for cyclobenzaprine in the United States, and during that time, Merck has distributed over 1.5 billion tablets in the United States. Since 1989, generic cyclobenzaprine has been available, so this is actually an undercount of the amount of cyclobenzaprine tablets that have been used. As Dr. Hemwall mentioned, we've had 993 reports of spontaneous adverse experiences reported to us. Two hundred and thirty-eight of those reports met the regulatory definition in effect at that time for what a serious adverse experience would be. Most of the adverse experiences related to the central nervous system, which is not surprising given the safety profile of the drug in clinical trials and the known pharmacologic effects.

Unfortunately, our WAES database does contain 52 reports describing 65 patients who died while taking or after taking cyclobenzaprine. Reviewing these 65 patients shows that there were 15 reports describing 22 patients who intentionally overdosed with the product. There were three reports of fetal death after a mother had taken cyclobenzaprine at some point during her pregnancy. But in the remaining reports, there was no clear pattern to suggest that cyclobenzaprine was causally related to the deaths. The majority of the reports, 29 to be exact, were confounded by the presence of underlying diseases or the

use of other medications. There were six patients with underlying heart disease, four with pulmonary disease, three with hepatic disease, three with cancer. Clearly, a spattering and a cross-section of concomitant illnesses that do not indicate a clear pattern.

We have gone and looked at the FDA's spontaneous report system database to see what is in that database concerning cyclobenzaprine, and we are aware of 25 reports of death that did not originate from Merck that are in those databases. Twenty-one of the 25 reports have been available to us already for review through the Freedom of Information, and we know within those 21 reports that there are five duplicates within the 21. We also know that two of those reports have also been sent in by Merck. So within the 21 reports we've been able to review, there were 14 unique patients that Merck was not aware of. They may have been reported by other manufacturers of generic products, or they may have been reported by manufacturers of other ethical products that the patients were using concomitantly.

There were five overdoses in the 14 reports, two fetal deaths, three heart attacks, and a spattering of other diseases. So again, within the FDA's database, looking at reports that did not come from Merck, no consistent pattern to suggest causality.

We know that cyclobenzaprine is chemically related to amitriptyline, a drug that is associated with cardiac arrhythmias and seizures in overdose. We have examined the available data to determine whether cyclobenzaprine is associated with life-threatening arrhythmias or seizures in either therapeutic use or overdose. The WAES database contains 16 reports of life-threatening dysrhythmias, which we classify as ventricular tachycardia, ventricular fibrillation or cardiac arrest. Eight of those patients died and were included in the summary slides I just presented. Of the remaining eight cases, there were two reports of ventricular tachycardia or fibrillation occurring during surgery, one in a patient who received droperidol, and one who was in septic shock undergoing an exploratory laparotomy. There were five reports of cardiac arrest with little information available, except in one case we know that there was a documented mycoplasma infection which may have been associated with a heart block, and there was one non-fatal overdose with several other drugs.

We've looked at the FDA's SRS database and we found three reports of life-threatening dysrhythmias that did not come from Merck and were entered in the database. There was a fatal overdose with other drugs, including oxycodone and acetaminophen, a person who developed chest