**Eli Lilly & Company**
**Zyprexa FDA Approval**
**October 1, 1996**



OPR: Good afternoon ladies and Gentlemen and welcome to the Lilly Zyprexa FDA approval conference call. At this time all participants are in an interactive mode. To ensure best audio quality, please keep all background noise to a minimum and utilize your view button if available. To utilize the self-mute feature, please press the star and six to meet your phone and to interact just press star and six again. Should anyone require assistance please press the star followed by the zero on your touchtone phone. I would now like to introduce your host for today's conference Miss Lori Roberts, Public Relations Spokesperson. Please go ahead ma'am.

LORI: Hi, this is Lori Roberts and I'd like to thank everyone for calling in today. I want to introduce everyone to Dr. Gary Tollefson. He is the Vice President of Lilly Research Laboratories and head of that ~~Atlanta~~ Olanzapine Heavyweight Team and I'll let Gary make a few statements and we'll open it up to questions. Thank you.

GARY: Thanks Lori, I appreciate all of you spending a few moments to share the good news of the Zyprexa story with us. Brief review of the chronology as you know, last September 22nd the company submitted both in Europe through the new centralized process and in the U.S., the docea for the approval of Zyprexa. Last Friday we received European

approval for the 15 member state and as you all know, last evening approval from the FDA, so essentially in a one year time frame. The situation, if I can give you a brief summary of our position I think relative to labeling, we're very, very pleased with the labeling that we've received both in Europe and in the U.S.. The labeling starts out by identifying the unique pharmacology of Alandzapene or Zyprexa and how that would be differentiated from the conventional products that are in the marketplace. it then goes into identifying that the indication for this compound is as an anti-psychotic agent, but with its specific focus, reflecting the clinical trials schizophrenia and it includes a recognition that Zyprexa has been shown relative to placebo to be statistically and significantly more effective, not only in positive symptoms, the conventional delusions and hallucinations of these illnesses, but also the so called deficit or negative symptoms that are really the prime drivers of individual disability and long term healthcare cost. The data is very consistent with the ability to maintain these acute therapeutic effects over at least one year and this is very important because schizophrenia is both a chronic and a relapsing condition. So the maintenance efficacy and the maintenance safety are also important factors. The key advantages that we see Zyprexa bringing to the marketplace relative to both the

Both label issue

older agents and those other new compounds in development is that with Zyprexa not only are we seeing a broader profile of efficacy, but we're also seeing a marked improvement in safety. For clinicians that means an improved risk benefit ratio. That is, better therapeutic gains and less risk of adverse events and this is very important in this patient population because well over half will discontinue their drug therapy, the older agents, because of adverse events. In our clinical trials experience, the number of patients who dropped out due to side effects on Zyprexa was actually numerically less than what we saw in patients taking placebo. The key area in defining a new anti-psychotic is looking at the drug's ability to not induce what are called Parkinsonian or motor signs and symptoms. Over 90% of patients on older conventional drugs will have these side effects and they are a prime determinant of why patients stop their treatment, become non-compliant and in turn, relapse. We're very pleased that the labeling in the U.S. will show by objective rating scales that both Parkinsons like side effects and restlessness or Acathisia, the incidence across all doses of Zyprexa was comparable to placebo. That is essentially this drug did not induce persistent Parkinsonian problems. We also are interested because from the viewpoint a the womens health perspective with the older drugs, they're known to chronically elevate a

body hormone called prolactin. Prolactin elevation is associated acutely with sexual dysfunction, but in the long term has also been associated with a higher risk of osteoporosis. In our labeling it will be clear that Zyprexa is not associated with these persistent high, long term elevations of prolactin, unlike a number of the older products and for that matter Respiradome. With some of the other agents, such as Clozapine or clozaril that you may be familiar with, of course there are prerequisites for blood monitoring on a weekly basis because of some of the safety concerns with those drugs. Of course is very troublesome to patients and very costly. We're very pleased that we have no requirements for any type of blood monitoring with Zyprexa. Another very important area is I think is that with long term use of these older agents, another concern for prescribers and patients would be the onset of what has been referred to as tartadisconnesia. Tartadisconnesias are persistent and often irreversible neurological movement disorders that are cosmetically quite disfiguring and also carry a number of health risks with them and in control trial data that we have presented in scientific fura, we've been able to show that there is a statistically and significantly lower incidence of this neurological side effect with Zyprexa then with conventional drugs. I'll finish with two final points in the label that I think are

especially important, because patients with schizophrenia are often likely to be taking multiple agents, at least more than one drug, the risk of drug drug interactions has always been a concern for prescribers and Zyprexa is a unique molecule in that it is a compound with very, very low risk for drug, drug interaction. This is something that will be featured or highlighted in the labeling. Lastly I think particularly important to the prescriber and patient, unlike make of the anti-psychotics currently in the marketplace that require the prescriber to start with very low doses that are subtherapeutic because of safety concerns then gradually work the patient into a therapeutic range where they can begin to get benefit, Zyprexa will have a starting does on day one of ten milligrams, which is also an effective therapeutic dose. So the bottom line is, there is no need for this historic, mandatory titration of drug. We can start with the therapeutically effective does on day one. So this overall profile and why we're excited about the molecule is what it really will mean for schizophrenic patients and that is a market improvement in its so called, risk benefit ratio for drug treatment. Broader efficacy, very attractive safety profile and in turn better compliance and because this is a chronic relapsing condition, compliance is essential. And we have been able to show in one year controlled trials that our rate of

rehospitalization or recurrence of psychosis was significantly less than what the most currently popular anti-psychotic Haldol. So hopefully that will give you a feel for the database and I guess I can add one other feat to that and that is that we also have evaluated quality of life in these patients because as much as we can look at the improvement in clinical rating scales, what really will drive having an innovative pharmaceutical is that patients and their caregivers perceive that the drug has led to an improvement in their quality of life and their functional well being. Using structured sales to access those aspects of quality of life, we're also able to show that they're statistically and significantly greater improvement in quality of life, including such important things as interpersonal relationships with Zyprexa. So that whole package is why I think we are very excited about what this molecule can mean for a disease that's been referred to in the psychiatric community as the cancer of psychiatry, schizophrenia.

LORI: We'll open that up for questions now.

... How do you go about doing that?

JAMIE: Gary?

GARY: Yes.

JAMIE: Hi, it's Jamie Tallon.

GARY: Hi.

JAMIE: Could you just give some statistics on the compliance and the quality of life. You said you did a comparison of with Haldo, what were the numbers on that?

GARY: Right, we had with Zyprexa treated patients over 95% of patients for example in the first six weeks when side effects are usually more prevalent, that were able to continue treatment and that was statistically significantly greater than what we saw with Haloperidol where we saw frequently more discontinuations, not only for side effects, but also for a lack of efficacy or the patients general sense that I just don't like taking this drug. In other words, at the patient's discretion.

JAMIE: What were the numbers with Haldol?

GARY: Well it looks, essentially we're talking about a 95% versus upper 80's percent out through six weeks. I think where the data increasingly becomes perhaps more interestingly is even those patients that were able to stay on treatment for six weeks, if you then follow them out, which we did under a double blind method for the next 52 weeks. We had statistically and significantly more patients that maintained their acute therapeutic improvement and did not have a clinical relapse. There we had about a ten to twelve percent advantage. So for every 100 patients, ten or 12 patients more who failed to have a clinical relapse.

JAMIE: Do you have numbers?

GARY: On which specifically?

JAMIE: On 52 weeks, how many of them relapsed versus the Haldol patients?

GARY: Yeah the numbers on the relapse rates are essentially about 92% versus approximately 80%. On the quality of life dimensions, again the key thing there that was statistically significant was the overall assessment of quality of life, but then very specifically the quality of interpersonal relationships that the patients experience as well as their cognitive abilities, some of their processing.

JAMIE: What about the side effect that I'm hearing about, weight gain?

GARY: Well weight gain has been something that's been reported with this whole class of medications and it's associated with the blockade of a receptor called the serotonin receptor and it was assumed to be just something that went along with this whole class of drugs. However we recognize being aware of the clinical situation, many psychotic patients who come into the hospital, come in being very nutritionally compromised, often significantly below their ideal body weight because they haven't been taking care of nutrition or personal hygiene. So we went back and analyzed our data and saw that the vast majority of weight gain reported initially as an adverse event, in fact, was weight gain occurring in patients who had baseline before

starting treatment, had been below their ideal body weight. So we really look at this in the majority of patients as being part of a therapeutic recovery rather than an adverse event. That data I think was fairly compelling because it was included in our labeling.

OPR: Do we have another question?

CHRIS: This is Chris O'Malley from the Indy Star, just was wondering is this product one of the fastest to come to market? In other words, to hit the store shelves, I think you're projecting late this week.

GARY: Well I think certainly for us, what we've done with this product is really reengineer the entire drug development process with what we call the heavy weight team, which a model that Steven Willright a Harvard Economist has written about. First of all I think we essentially have been able to shave about 18 months in the overall drug development scheme of by essentially being more efficient in what we have done. Now part of that is to also be more effective with the actual global launch and that is, how quickly does drug reach a pharmacist shelf, so it's available to patients after receiving regulatory approval. Traditionally that could have taken weeks, literally weeks for us and for other companies. When it came to Zyprexa to give you some examples, in the United Kingdom when we received approval on Friday from the European Medicines

Agency we had drug available for patients in the hospital an hour and five minutes after approval. Here in the U.S, we expect to really have drug available somewhere in the time frame of about 48 hours after approval. So this does represent a very significant reengineering of the process. Let my just add that the importance of that, obviously it has added some value to the company and the company shareholders, but the key driver here is that schizophrenia is a serious disease with morbidity and mortality and the sooner we feel we can get this innovative drug in the hands of patients, the better off we are as far as public health good.

KEVIN: Doctor Tollefson, this Kevin Draub with Reuters. Can you tell us a little bit about the clinical trials your projecting, matching Zyprexa against some of these other new atypical anti-psychotics?

... Like Clozapine.

KEVIN: Yeah.

GARY: Sure, we have several underway. Actually we had a head to head try which Speridin is near completion and we would plan to have that data available for publication in December of this year and feeling I think, very encouraged to day with where that study has been headed. We also have in Europe several multi-national studies that are head to head comparison against Clozapine. They will probably be

completing in a similar timeframe and last but not least in the U.S. relative to Clozapine we have a study going on which is really investigating the concept of crossing patients from Clozapine who haven't done well because of safety concerns or lack of efficacy over to Zyprexa and A, how should that be done and then B, how effectively is Zyprexa as a cross over therapy. That's modeled after a very positive study experience we had in Israel with a study sponsored by the Ministry of Health there, where patients who were really having problems with Clozapine were crossed over to Zyprexa and had a very nice clinical outcome. So that has set the stage for some of these head to head trials all under what we call a double blind to maximize the scientific validity of the data.

KEVIN: And the U.S. _____ study results will be coming a little later then.

GARY: Those are all targeted for the later part of Q4, that's right.

KEVIN: Thank you.

GARY: If I could, I wanted to just clarify on the maintenance data numbers because I think I may have given you the wrong number. The maintenance of acute therapeutic effects for Alandsapene were approximately 81%, versus approximately 70% for Haloperidol and that was again, a statistically significant difference. So if I said a wrong

number there, I apologize.

JAMIE: What was that again Gary, I'm sorry?

GARY: Yeah 81 versus 71.

JAMIE: For what?

GARY: Alandsapene maintaining acute therapeutic effects versus Haloperidol. Thanks.

OPR: Do we have any more questions?

JAMIE: Do you envision having any problem? Clozapine had a lot of problems in states getting access to the drug for patients. I don't think it was a problem with Sandos, I think it was a problem with the state, State Regulatory Agencies. Do you envision such a problem or was that because of the agranular sytosis problem?

GARY: Well a little bit of both. That's a good question. We certainly did envisions of the problem as one that could be out there and we looked at that about a year ago and we began working with our managers of public affairs to start having discussions with state legislators relative to medicaid, as well as a number of the large formularies to begin to educate them about the direct and indirect healthcare costs that schizophrenia and in fact the value of innovative pharmaceuticals. We've been able to make some significant inroads already in most of the major states regarding their appropriations for novel anti-psychotic medication. So we think that that's sort of health

economics and resource utilization story based on our Zyprexa database has been a compelling factor. The good new is we started that work over a year ago, so the market I think is prepared now for Zyprexa and the drug I think, will not be limited in availability to those patients. The issue around Clozapine you're absolutely right though, because in addition to the pharmaceutical acquisition cost with Clozapine, one has the very expensive mandatory laboratory monitoring on a weekly basis that made in some states the drug either cost prohibitive or it severely restricted those patients who could have access to it. Comparatively speaking, obviously Zyprexa should be available to a much larger spectrum of patients.

JAMIE: Do you envision first line therapy for new, first time episodes and how much is it going to cost?

GARY: Well as far as the first line therapy component, we certainly do. We did do trials and what are called first episode or first break patients and showed even more dramatic advantages over a standard comparator agent then we same in the chronic patients, so we're going to take an approach that looking at the safety and efficacy profile of this drug, there's absolutely no reason in our minds that it should not be a first line treatment and sort of the approach will be that this compound has all of the desirable anti-psychotic properties or power of a drug like Clozapine

without the risk. So we're looking at this as routine daily use for this compound.

JAMIE: How much?

GARY: We think that the compound is going to be comparably priced to Risperidone at six milligrams in the marketplace and in most states, at least that I'm familiar with the pricing structure less than the drug cost for Clozapine.

JAMIE: How much, do we have any idea? A dollar a pill, two dollars a pill?

GARY: Well again the advantage of this drug is that there is no titration, so the routine starting dose on day one will be ten milligrams and as I say, it will comparably priced to Risperidone Six and it'll probably be in the ballpark of about $6.48 for one ten milligram tablet.

JAMIE: Maintenance dose, is maintenance dose the same or does it go down after the--

GARY: The maintenance dose in our controlled trials for the majority of the patients, about two thirds was exactly the same dose. In a few patients though clinicians did go down in dose. Because the drug was so well tolerated, many of the clinicians or investigators didn't feel a need to do down in dose because they were seeing good results and didn't really want to take the risk. If you look at the older anti-psychotic literature, because of the risk of

tartadisconnesia with those older drugs, people have made numerous efforts to try to cut back on acute therapeutic dose, but the problem is when they do that, they see a higher rate of relapse. So in general, the guidelines have been to try to use that acute dose for maintenance purposes if the patient can tolerate it. One of the nice stories with Zyprexa is that patients do seem to tolerate it quite well.

JAMIE: Thank you guys.

OPR: Do we have any more questions?

... Yeah, I just wanted to confirm that you're projecting the price of this ten milligram tablet about $6.48 each?

JAMIE: Forty cents.

GARY: Six four eight, that's correct.

... Yeah, 6.48. Great, thank you very much.

JAMIE: Gary?

GARY: Yes.

JAMIE: Are you going to be available in your office in a few minutes?

GARY: Well I do have a meeting, I could try to give you a call back.

JAMIE: Okay.

LORI: Who's this?

JAMIE: Jamie Tallon.

LORI: Okay Jamie, we'll try to get back to you.

JAMIE: Thanks Lori.

LORI: Happy to.

OPR: Do we have any more questions? Is there anyone else out there?

LORI: It's a wrap.

OPR: Okay, great.

... That's it I guess, thanks very much.

... Bye.

... Bye.