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CC: CN=Mark D Millikan/OU=AM/O=LLY@Lilly
Date: 04/18/2002 07:26:46 AM
From: CN=Patrizia Cavazzoni/OU=AM/O=LLY
Subject: Label changes for zyprexa READ THISONE FIRST

All

For regulatory agencies who have NOT been aware of olz glucose issue, it would be EXTREMELY important to FRAME the issue within the context of all olz and non-olz glu data. I would recommend that we DO NOT submit information on Japan without providing this context, with the exception of Regulatory agencies wher issue has been followed closely (ie FDA Neuropharm and CPMP).

Exec Summary of olz glu data (eg PCS, GPRD, HGIM summaries we prepared for last round with MHLW, maybe using letter Michele had prepared for last spring's FDA update??

For pm data, I would provide REPORTING FREQUENCIES rather than absolute numbers, including RF of all glu events, DKA events, and deaths related to glu events

We will also need this document for other nedical requests that have been coming in (eg istvan Bitter), ie for situation wher communication tone would lie somewhere between FDA/CPMP and standby satement

Thank you

Patrizia

----- Forwarded by Patrizia Cavazzoni/AM/LLY on 04/18/2002 06:17 AM -----

Elizabeth Brunner

04/17/2002 08:55 PM

To: Patrizia Cavazzoni/AM/LLY@Lilly
cc:
Subject: Label changes for zyprexa

Hello Patricia

Page: 1 of 2

I'm the CRP for NS in Mexico. I need to prepare a document for our loca regulatory agency to have in case we are questioned about the Japan label changes issue. I would like to speak to you...could you tell me when is most convinient for you tomorrow april after 12:00 pm. or friday?

Regards and thankyou

Elizabeth Brunner
CRP NS Mexico
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Page: 2 of 2

“Zyprexa” warning of administration to DM patient

- two patients died of coma ·conscience disorder due to increased blood glucose-

It was reported that 9 patients who have taken Zyprexa, schizophrenic agent had severe adverse events such as coma and conscience disorder due to increased blood glucose and 2 of them died in Japan for 10 months.

Japan press such as mainich newspaper announced that MHLW requested Eli Lilly to revise insert paper (contraindication to DM patients) and distribute urgent safety information to related medical centers on Apr 16.

According to MHLW, among 9 patients who had severe adverse events, which cannot deny the relation with the drug, two male patients was diagnosed as DM prior to administration of this drug, but dead two male patients did not have DM. But, both two men was obese or had tendency to weight gain.

Zyprexa has been launched since 1996 in US and it has been marketed in 84 countries until last September. In Japan, it has been marketed since last June and it is expected about 137, 000 patients have taken it until last December. Also, it alleviates pt's symptom such as delusion and hallucination and has a few adverse events such as tremor and dysbasia, which are inevitable in previous schizophrenic agent.

According to MHLW's request, Eli Lilly is planning to distribute urgent safety information to related medical centers as follows.

- Contraindication to DM patients or patients who has a history of DM
- Observe increased blood glucose carefully during administration
- Explain the possibility of adverse events to patient and his family

Also, according to Eli Lilly, increased blood glucose estimated as adverse event of Zyprexa have been indicated in 278 patients and 36 patients have been dead in foreign countries.

Urgent Safety Action on Zyprexa by KFDA
Addition of “Prohibition of Using by Diabetic patients”
according to Japanese death case

Korea Food & Drug Administration(KFDA) has decided to take urgent safety action of prohibiting prescription of Zyprexa for diabetic patients, this anti-psychotic drug, supplied by Eli Lilly and Company, had been reported to cause coma and consciousness impediment by hyperglycemia.

April 19th. 2002, one of KFDA official announced “we are investigating through Japanese embassy and foreign articles the safety action taken by The Ministry of Health, Labor and Welfare(MHLW) in Japan, prompted by 9 severe case reports of hyperglycemia, including two deaths from diabetic coma in last 10 months”, and “The same safety actions will be taken sooner or later in Korea”.

This official also said, “There’re some case reports that indicate the blood glucose level increase in obesity patients who have no diabetic symptoms, during prescription of Zyprexa”, and “through the changes in Zyprexa label, we will prohibit the prescription of this drug for diabetic patients, and for already prescribed patients compel to add notice that there should be a checks and control on increase in blood glucose level.”

By the way, Korean affiliate Lilly Korea Ltd. said, “based on current research articles, schizophreniac patients are in the high risks of diabetes regardless of the drug they use, and before fifty years when there’s no anti-psychotic drug, the patients indicated the high frequencies of diabetes by the factors like obesity, movement way and genetic factor.” And Lilly Korea also announced that Zyprexa is not a direct cause of diabetes.