

To: CN=Peter Beardsall/OU=EMA/O=LLY@Lilly
CC: CN=Peter Aitken/OU=EMA/O=LLY@Lilly; CN=Neil G Archer/OU=EMA/O=LLY@Lilly; CN=Michael E Bandick/OU=AM/O=LLY@Lilly; CN=Patrizia Cavazzoni/OU=AM/O=LLY@Lilly; CN=Matthew A Critchlow/OU=EMA/O=LLY@Lilly; CN=Bin Gu/OU=AM/O=LLY@Lilly; CN=Philip R Knott/OU=EMA/O=LLY@Lilly; CN=Louise Strong/OU=EMA/O=LLY@Lilly; CN=Hiram Wildgust/OU=EMA/O=LLY@Lilly
Date: 10/18/2002 10:03:49 AM
From: CN=Matthew R Pike/OU=AM/O=LLY
Subject: Re: Your input please !!

Peter,

I spoke with Patrizia Cavazzoni regarding the matter described below. Our thoughts are that it would be next to impossible to conduct a meta analysis of the various epidemiological studies because some use hazard ratios, some use odds ratios, they vary widely by what factors were controlled for, etc. Even if you could conduct the meta analysis, the likely outcome is a finding that risperidone carries the lowest risk. In the end, the meta analysis would be no more conclusive than the individual studies.

Alternatively, one could do more of a review article that critiques each of the studies and includes case reports, epidemiological studies, head to head trials and physiological clamp studies. This makes sense as complex issues such as this one cannot be thoroughly examined through one type of study. By defining the examination of the issue in this way, we can minimize the impact of any one negative study that may appear. Should Lambert publish his findings, one could argue that it is yet another prescription database review, one of many that have resulted in conflicting views. And in itself, it is insufficient to draw conclusions regarding this very complex issue.

To this end, Patrizia is currently working on a paper that would present some new data (reviving our GPRD study!) as part of a review of this issue from the broader perspective I have outlined above. We believe we can get it published in a psychiatry journal during Q1 of next year. We will try to address the concerns of external lead authorship as well.

As far as the Ereshevsky proposal is concerned I would like to raise 2 concerns. First is that the approach outlined above is one that essentially states that there is no one study that will resolve this issue. The second is that if he were to publish his proposed methodology (would he without our help anyway?) would we then be compelled to conduct the study? As Hiram pointed out, it would be a very lengthy and expensive trial, with outcomes we cannot necessarily predict.

I welcome your comments to this proposal.

Matt Pike, R.Ph.
Issues Management Manager
Zyprexa Global Marketing

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317-651-3990

Peter Beardsall

10/16/2002 08:41 AM

To: Louise Strong/EMA/LLY@Lilly
cc: Peter Aitken/EMA/LLY@Lilly, Neil G Archer/EMA/LLY@Lilly, Matthew A Critchlow/EMA/LLY@Lilly, Philip R Knott/EMA/LLY@Lilly, Matthew R Pike/AM/LLY@Lilly, Louise Strong/EMA/LLY@Lilly, Hiram Wildgust/EMA/LLY@Lilly
Subject: Re: Your input please !!

Dear Louise - Neil makes a great point here about "what to do in the meantime" I was wandering where your negotiations were at with the Medical Education firms and whether they could help us quickly ? Does anyone else have any ideas on this ?

cheers

pete

++++
Pete Beardsall
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++++

----- Forwarded by Peter Beardsall/EMA/LLY on 16/10/2002 14:39 -----

Neil G Archer

16/10/2002 13:14

To: Peter Beardsall/EMA/LLY@Lilly
cc:
Subject: Re: Your input please !!

Pete,

In my opinion, this is a "must do." Subject to the opinions of the other addressees, we should start the ball rolling here asap, as publication of such a paper is probably at least a year away.

In the meantime, how can we best manage the shorter term challenges that we face around the plethora of negative publications headed our way ?

Regards,
Neil.

Neil Archer
Business Unit Manager,
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Peter Beardsall

16/10/2002 13:10

To: Peter Aitken/EMA/LLY@Lilly, Neil G Archer/EMA/LLY@Lilly, Matthew A Critchlow/EMA/LLY@Lilly, Philip R Knott/EMA/LLY@Lilly, Matthew R Pike/AM/LLY@Lilly, Louise Strong/EMA/LLY@Lilly, Hiram Wildgust/EMA/LLY@Lilly

cc:

Subject: Your input please !!

Dear All,

ref the email below, I personally think that the time has come to push for a "stake in the ground" Meta-analysis of the huge pool of data surrounding the issue of diabetes and antipsychotics. Awareness and concern are at levels that I feel make "adding to the fury" a less relevant argument. The recent list of all studies relating to diabetes that are now out there is huge, and characterised by a significant weighting overall of those that do not support our position.

I would like to suggest that we now urgently embark on getting a credible "landmark" paper written and published. The critical success factors for such an article to me seem to be

1 - Published somewhere impactful - e.g. Lancet

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- 2 - Written by someone who we know to be supportive of our position, but who is also clearly independent of us and above all CREDIBLE
- 3 - The core conclusions of the piece most relevant to our position should be
 - any association is of minimal clinical significance due to the widely documented low levels of incidence
 - where diabetes, or any other disease happens to occur to someone with schizophrenia (as will obviously happen), it should be managed as it would be for someone who does not have schizophrenia.
 - diabetes is seen more often with those with schizophrenia, and so confidence in managing it should be routine to the disease area.
 - the risk of any increase in association is equivalent across anti-psychotics, and the awareness / concern should be relevant to all anti-psychotics
 - data that shows lower prevalence in one antipsychotic than another CANNOT be used to make comparative risk assessments, especially for those treatments that have lower usage bases, or no usage bases (eg aripip). Attempting to do so borders on unethical as it would potentially put patients at risk of not being on treatments most able to control their symptoms.
- 4 - The paper needs to be a full meta-analysis of all the data. This would therefore be superior to any one study when thinking of future ABPI challenges.
- 5 - We must chose a publication route that will deliver something in print as soon as is possible, without comprising the above.

Team - what are your thoughts - is this a good idea ?

Pete

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----- Forwarded by Peter Beardsall/EMA/LLY on 16/10/2002 12:50 -----

Hiram Wildgust

14/10/2002 20:38

To: Neil G Archer/EMA/LLY@Lilly
cc: Peter Beardsall/EMA/LLY
Subject: POSTER ON RISK OF ANTIPSYCHOTIC INDUCED TYPE DIABETES (BRUCE LAMBERT)

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Neil,

I think addressing this poster and potential publication is difficult (I have put in red my responses to your questions).

My personal belief here is that to minimise the damage from this type of publication requires a high quality publication describing a study design which will answer this question of risk of induction of type diabetes through treatment ... it would describe a prospective study design, large numbers of patients, controlling for ethnicity, obesity, genetic predisposition, where blood glucose levels are routinely measured, etc.... and in the discussion, this paper could critically comment on data generated from non-prospsective studies, In summary, this paper, would set the bar as to what was a good study and challenge strongly data from studies which do not have the appropriate study design? I will discuss this with Peter B. Potentially, Larry Ereshefsky (professor pharmacuy Psychiatry at Texas might be able to write such a paper). I discuss ed this topic with him at ECNP and the above thoughts very much mirrored his view point).

Your help may be to energise the US to take action, and learn from Davos. I hope my thoughts are helpful

Regards
Hiram

Neil G Archer

14/10/2002 17:26

To: Hiram Wildgust/EMA/LLY@Lilly
cc: Annie F Creo/EMA/LLY@Lilly
Subject: Re: Barcelona air traffic control.

Hiram,

I like your suggestion re: a brief synopsis of each customer to provide back to their local representative, as I do a distillation of the salient competitive points.

The Lambert poster is a concern. If we work on the assumption that this poster WILL be published as a full manuscript soon, our attention needs to turn to how we can minimise its impact on both the global and local level. It would be worth suggesting to Peter B. that we loop in the Product Team's thinking asap on this one, although we may be able to actually act far quicker if we implement our plans locally.

Questions to consider, beyond the usual responses to such an issue:

Where will this paper be published ? ? **difficult to say..... US pharmacy pratice journal, american journal of psychiatry .. just**

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guessing

Can we stop / delay it ? I think it would be very difficult to delay, except if one of our scientists could show them that their whole methodology was flawed (? richard Petty USA) Larry Ereshefesy

What can we do to ensure that the robustness of this science vs other methods is understood by its audience ? (we need to have a paper published which reviews this whole topic focusing on methodology and exposing the inadequacies of retrospective data trawls..... although patients matched for ethnicity, no comment on obesity, family history ...only large scale prospective studies will answer this question of risk

Do we know the author ? Can we exert any influence ? this would be very dangerous as it would be seen as lilly behaving unethically and this applies to the below points

Who sits on the editorial board of the targeted journal ? Can we influence them in any way, with respect to the limitations of this methodology ?

Should we conduct a communications initiative aimed at all influential referees, addressing the above point ?

There are many more - these are some top of the head thoughts. Please let me know how I can help.

Regards,
Neil.

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Hiram Wildgust

14/10/2002 17:00

To: Neil G Archer/EMA/LLY@Lilly
cc: Annie F Creo/EMA/LLY@Lilly
Subject: Re: Barcelona air traffic control.

Neil,

It was a great pleasure to have your support at ECNP and both Annie and myself are pleased you missed the fun and games at the airport.... what airport ? . Thank you for your kind words about our support.

There is a potentially an enormous amount of information to share with our colleagues. My thoughts are to give appropriate posters to Peter Beardsall, Phil Knott and David Mcgee, with brief emails to each about important events and also feedback to local managers about delegates from their region. I welcome your thoughts here.

One poster which caused me great concern was by Bruce Lambert 'titled' assessing the risk of antipsychotic induced diabetes among schizophrenics: A matched case control study (Bristol Myers sponsored). This study is one step up from Koro, data base study, as it claims to control for ethnicity and exposure to other diabetes -inducing medication (looks at clozapine, olanzapine, quetiapine and risperidone) Conclusions was that exposure to clozapine, olanzapine, and quetiapine but not risperidone was associated with a significant risk of developing type 2 diabetes when compared to typical antipsychotics. I flag this up as almost certainly this poster will be published and raise the noise around diabetes and olanzapine. This type of study (data base) cannot accurately collect data about the risks because it is not prospective, blood glucose levels are not measured. I will discuss this with Peter Beardsall as we need to get the US team on to this before it is published.

Cheers

Hiram

Neil G Archer

14/10/2002 09:38

To: Annie F Creo/EMA/LLY@Lilly, Hiram Wildgust/EMA/LLY@Lilly
cc: Philip R Knott/EMA/LLY@Lilly, Ian Knowlton/EMA/LLY@Lilly, Claire Munkley/EMA/LLY@Lilly
Subject: Barcelona air traffic control.

Annie, Hiram,

The phrase "Spanish air traffic control" must now have extra meaning for you !

Prior to events of Wednesday, I'd seen you both do an outstanding job in marshalling us all through ECNP in a very professional and credible way. After the rains fell, even more credit is due to you for not only putting up with a very trying set of circumstances yourselves, but for managing the whole situation and large group of customers in the most professional way. Its times like these that seperate the "average" from true winners and you very firmly placed yourself in the winner's camp last week.

Thanks - for a great job and a top outcome from ECNP.

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Regards,
Neil.

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