My input on this issue to Dave Brockwell this morning was that we should be consistent with and not arguing contrary to the SPC warnings, section 4.4, or Section 4.8 (undesirable effects) both of which which I quote below:

from Section 4.4
"Hyperglycaemia or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma has been reported very rarely, including some fatal cases. In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus."

The main difference between this and the MCA statements below is that we say the dka or coma is very rare. This is backed up by section 4.8. Also, we do not actually cite diabetes per se as an ADE - but if we raise this explicitly we may encourage UK CPMP delegates to request this!

In Section 4.8 in the CT ADE table we do have "Common (1-10%): Elevated glucose levels (see note 1 below)" with footnote 1 "In clinical trials with olanzapine in over 5000 patients with baseline non-fasting glucose levels 7.8 mmol/l, the incidence of non-fasting plasma glucose levels 11 mmol/l (suggestive of diabetes) was 1.0%, compared to 0.9% with placebo. The incidence of non-fasting plasma glucose levels 8.9 mmol/l but < 11 mmol/l (suggestive of hyperglycaemia) was 2.0%, compared to 1.6% with placebo. Hyperglycaemia is also reported as a Very Rare (<0.01%) spontaneous event."

And in the PMS ADE Table we also have "Very rare (<0.01%): Hyperglycaemia or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma has been spontaneously reported very rarely, including some fatal cases (see also Note 1 above and Section 4.4, Special warnings and special precautions for use)."

John Saunders
European Regulatory
Phone: 44 (0) 1276-483381

Anna R Thornton
17/12/2001 15:34

To: John C Saunders/EMA/LLY@Lilly
cc: Peter Aitken/EMA/LLY@Lilly, Neil G Archer/EMA/LLY@Lilly, Suzanne H Barrick/AM/LLY@Lilly, Peter Beardsall/EMA/LLY@Lilly, Christopher Carlson/AM/LLY@Lilly, Patrizia Cavazzoni/AM/LLY@Lilly, David G Perahia/EMA/LLY@Lilly, Alexander Simpson/EMA/LLY@Lilly, Anna R Thornton/AM/LLY@Lilly, Padraig Wright/EMA/LLY@Lilly
Subject: Re:Upcoming UK MCA article on olanzapine and glucose monitoring

John,

Your insight is greatly appreciated!

Please feel free to contact me if you would prefer to discuss,

317-277-7076.

Regards,

Anna

----- Forwarded by Anna R Thornton/AM/LLY on 12/17/2001 10:31 AM -----
Peter Aitken
12/17/2001 10:28 AM

To: Patrizia Cavazzoni/AM/LLY@Lilly, Padraig Wright/EMA/LLY
cc: Neil G Archer/EMA/LLY@Lilly, Suzanne H Barrick/AM/LLY@Lilly, Peter Beardsall/EMA/LLY@Lilly, Christopher Carlson/AM/LLY@Lilly, David G Perahia/EMA/LLY@Lilly, Alexander Simpson/EMA/LLY@Lilly, Anna R Thornton/AM/LLY@Lilly
Subject: Re:Upcoming UK MCA article on olanzapine and glucose monitoring

Patrizia,

Thanks for this and also for sending on the conference posters. We'll have all the evidence options to disucss tomorrow and respond to the MCA by their timeline.

For those who haven't seen their planned paragraph here it is verbatim. This will go by post to all UK doctors in January 2001:

Olanzapine (Zyprexa) and diabetes

Clinical Monitoring recommended in diabetic patients

Olanzapine (Zyprexa), an atypical antipsychotic, is indicated for the treatment of schizophrenia. Cases of diabetes mellitus, hyperglycaemia or exacerbation of disease, associated with ketoacidosis or coma, including some fatal outcomes, have been reported through the Yellow Card scheme.

In some cases, a prior increase in body weight has been reported which may be a predisposing factor for hyperglycaemia or exacerbation of pre existing diabetes.

Therefore, prescribers are reminded that in diabetic patients, or those with risk factors for diabetes, appropriate clinical monitoring is advisable.

Padraig, thanks for your advice.

Peter

Sandy and I ahve attempted to talk about this by 'phone but without success as cannot connect in real time

However, I think that you are as up to speed on teh issue as I am. I am not quite suure what MCA plan to say but from your e-mail it would appear to highlight glycaemia as a particular problem for olanzapine and this, as far as we know, is not the case.

In terms of a response, I would suggest that the planks of our argument come from the PCS database and the DSRU database. The mss. from latter has just been published as you know in J Clin Psychopharm nad is UK data, the PCS while US data is powerful in so far as it represents data from 5.8 million general population, 20,000 typical and 40,000 atypical patients

IN my view the structiure of your response should be something along the lines of

DM common in general population
risk of DM incereaed with schizophrenia
risk of DM increased further with schizophrenia treated with antipsychotics
we have evidence from 3 sources that risk is no higher with olanz than any other atypical (cloz an exception) or typical antipsychotic viz. (1) own DB CTs of olz v risp and olz v hal (statistical diff but not clin signif), (2) DSRU UK database and (3) PCS database.
QED - no reason to single olz out as needinf specila monitoring in pts with DM etc.

Where should the clamp study data go? I am not sure and maybe should be excluded,

Another point - although we have data that suggest risp may be more of a riosk rthan olz for DM etc. i don't think it would help to make thsi point - I think we are more likely to 'win' the point that olz carreis no more risk of DM than others

Call me if you need help

Padraig

Kathleen Fowler advises only one death, so they cannot justify 'some fatal outcomes.

Patrizia Cavazzoni
17/12/2001 14:11

To: Peter Aitken/EMA/LLY@Lilly
cc: Neil G Archer/EMA/LLY@Lilly, Suzanne H Barrick/AM/LLY@Lilly, Christopher Carlson/AM/LLY@Lilly, Alexander Simpson/EMA/LLY@Lilly, Anna R Thornton/AM/LLY@Lilly, Padraig Wright/EMA/LLY@Lilly
Subject: Re:Upcoming UK MCA article on olanzapine and glucose monitoring

Peter

I agree that it would be important to saher the UK GPRD data with the MCA, as long as we are all in agreement. If we decide to share data with UK MCA, I would suggest we show them poster that was presented at the ACNP. This would have the added advantage of allowing them to reference the ACNP presentation in their article, if they wished. Also,you may want to show them the PCS data (WCBP poster), we also have a manuscript that could be shared confidentially. Also, the results of the hyperglycemic clamp study may be of help in "leveling the field" with risperidone.When it comes to the sharing manuscripts, I am always somewhat concerned about jeopardizing

publication. However, if you think sharing manuscripts in confidence in addition to posters (which could be referenced in the MCA publication) would strengthen our position, please let me know

Padraig

Do you have any additional thoughts, in light of the comments you sent me?

Suzanne and Chris

While we wait to hear back from Peter re. manuscripts, could you please send Peter electronic copies (Powerpoint and PDF) of the following
1) PCS poster presented at WCBP (Suzanne)
2) UK GPRD poster presented at ACNP (I am not sure if we have PDF yet, if not, pls send Powerpoint) (Suzanne)
3) HGIM poster presented at ACNP (Suzanne)

Anna

I am copying you FYI

Thank you

Patrizia

Peter Aitken
12/17/2001 05:36 AM

To: Patrizia Cavazzoni/AM/LLY@Lilly, Padraig Wright/EMA/LLY
cc: Neil G Archer/EMA/LLY, Alexander Simpson/EMA/LLY@Lilly
Subject: Re: Revised UK-GPRD poster and manuscript

Patrizia,

This is excellent and very timely.

I shared the one slide highlighting the risperidone cases to our last opinion leader board of the year and it changed minds around the table. They had no idea this could be an issue for risperidone.

We have today received notification from the MCA that they will publish a paragraph entitiled Olanzapine and diabetes in their monthly publication to all UK doctors, it is recommending clinical monitoring in diabetic patients and those considered to have risk factors for diabetes.

Given the lack of evidence to present to the MCA the UK GP RD database data would greatly strengthen our case for their article to be broadened.

Can I share the paper in draft with the Uk MCA in confidence at this time?

The UK affiliate regards this as business critical as this endorsement by the MCA would carry maximum weight with opinion lead, clinicians and our competitors?

Can you let me know today as our MCA timeline is 1200 UK time Thursday.

Regards

Peter

Patrizia Cavazzoni
14/12/2001 20:48

To: Peter Aitken/EMA/LLY@Lilly, Walter Deberdt/EMA/LLY@Lilly, Padraig Wright/EMA/LLY@Lilly
cc:
Subject: Revised UK-GPRD poster and manuscript

I am forwarding a revised version of the manuscript. As you can see, much work has gone towards addressing the concernes that were raised in the llast round of e-mail traffic. We ran additional analyses on the cumulative antipsychotic data (ie conventional + atypical), and are presenting incidence and risk of DM in cumulative AP vs general population (rather than conventional vs atypical vs gen pop). Following addiotal discussions, we decided to forgo Lancet, and are planning to submit to BJP (given focus on UK-GPRD and external UK thought leader as senior author)

Please let me know your thoughts

Regards

Patrizia

[attachment "GPRD BJP 12-10-01.doc" has been removed by Peter Aitken/EMA/LLY]